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Paul Galpin Shipley

October 17, 1888—September 12, 1934

The Editorial Board of the BULLETIN OF THE JOHNS HOPKINS HOSPITAL records with deep regret the death of Dr. Paul Galpin Shipley on September 12, 1934. A member of the board since 1927, Dr. Shipley gave willingly of his time and energy to his editorial duties.

After being graduated from Yale Medical School he became associated with the Department of Anatomy in Johns Hopkins University School of Medicine under Dr. Mall. His studies upon the structure of developing tissues, particularly of bone, led to his transfer in 1917 to the Department of Pediatrics under Dr. Howland. He contributed much to the experimental observations upon rickets conducted by members of this department and devised a technique making it possible to produce and to follow calcification of bone *in vitro*.

His bibliography includes publications upon the demonstration, by spectrographic methods, of lead in the blood and upon infectious diseases. He was among the first to recognize Tick Fever upon the Atlantic Seaboard. Deeply interested in the history of medicine he contributed several papers in this field.

Throughout his career in pediatrics he was engaged in clinical observation and in teaching. He will be remembered by his students and colleagues as a vivid personality. With his death the members of the Editorial Board have lost an able and congenial co-worker.

STUDIES ON THE PHYSIOLOGY OF THE PARATHYROID GLANDS

VII. Some Responses of Normal Human Kidneys and Blood to Intravenous Parathyroid Extract

READ ELLSWORTH and JOHN EAGER HOWARD

From the Chemical Laboratory of the Department of Medicine, the Johns Hopkins Hospital

Submitted for publication August 29, 1934

In previous reports (1) (2) it was shown that the intramuscular injection of parathyroid extract in patients with hypoparathyroidism was followed by an outpouring of phosphorus in the urine. This effect took place within an hour after the injection and was attended by a fall in the inorganic phosphorus of the serum. The promptness and regularity of the increase in urinary phosphorus excretion, together with the well known interrelationship of the metabolism of calcium and phosphorus suggested that the increased elimination of phosphorus in the urine might be a primary and fundamental effect of the parathyroid hormone. In order to test further this hypothesis, the present experiments were arranged. The salient facts that we wished to ascertain were, first, whether the increased excretion of phosphorus in the urine, previously observed in patients with hypoparathyroidism, would occur regularly in normal individuals, and secondly, if it did occur, whether there was an associated change in the calcium and inorganic phosphorus levels of the blood. Furthermore, in order to throw more light upon the nature of the increase in urinary excretion of phosphate, observations upon urine volume, urine chlorides, urine pH and urea clearances have been made. These latter observations were made simultaneously, and with, the same urine specimens, as were used for the phosphate determinations. To avoid the criticism that intramuscular injections *per se* might influence phosphorus metabolism, and also to sharpen the point between control and experimental periods, the parathyroid extract was given intravenously.

The data presented here represent single experiments upon six "normal" individuals and three experiments upon one patient with hypoparathyroidism. For the so-called normal individuals, patients were selected who were convalescent from an acute illness and who, while under observation for some time, had shown no evidence of renal or metabolic disease.

PROCEDURE

All subjects were kept fasting and at rest for 16 hours before and also during the first six to eight hours of the experiment. The fluid intake during the time of the experiment is shown in table 4. Urine samples were collected hourly for 3 hours before and for 3 to 5 hours after the injection of the parathyroid extract. Blood samples were taken before and at various hours after the injection, as shown in the tables. Two cubic centimeters (40 units) of parathormone[1] were diluted to 10 cc. with normal saline and injected intravenously. A single injection was employed in each experiment. No untoward reactions were observed.

Standard analytical methods were used. For plasma and urine phosphorus the methods of Fiske and Subbarow (3) were employed; for calcium in serum and urine the Kramer-Tisdall methods (4) (5); for chlorides in urine, a modified Volhard-Harvey titration (6); and for urine pH the quinhydrone electrode.

RESULTS

Urine phosphorus

The hourly rate of excretion of phosphorus in the urine in the normal individuals, both during the hours of control observation and after the parathormone injection, varied over a wide range. In each case, however, the outpouring of phosphorus in the urine, following the injection of parathormone, was very striking. This is shown both as total milligrams per hour and as "phosphorus clearance" (cc. plasma cleared of phosphorus per hour) in table 1. The patient with hypoparathyroidism (tables 1 and 2) had been kept on a low-phosphorus diet and the urinary excretion of phosphorus during the hours of control observation was extremely low. Following the injection

[1] Collip's extract prepared by Eli Lilly and Company.

of parathormone there was a sudden rise from the very low level to a high hourly rate of excretion of urinary phosphorus. The hourly

TABLE 1

TIME	SUBJECTS—NORMAL						HYPOPARATHYROIDISM
	Henry C.	Robt. C.	James R.	Sam W.	Thomas S.	F. F.	Helen C.†
Urine phosphorus, mgm. per hr.							
7–8	16.8	5.4	12.4	18.9	20.0	29.2	0.2
8–9	9.1	7.5	11.8	24.4	23.4	32.6	0.2
9–10	12.5	12.0	8.8	28.0	21.0	43.0	0.2
	Parathormone 40 u. i.v. at 10 A.M.						
10–11	42.2	56.0	48.2	42.2	47.0	113.0	11.5
11–12	51.5	69.0	42.8	61.0	*	118.0	61.2
12–1	41.0	73.5	82.8	51.0	59.0	99.0	61.9
Plasma inorganic phosphorus, mgm. per 100 cc.							
9.00 A.M.	5.3				4.8		5.8
10.00		4.0	3.8	4.0		4.6	
	Parathormone 40 u. i.v. at 10 A.M.						
11.00 P.M.	5.2	4.0	3.3				5.3
12.00	4.9	4.0	3.2				5.0
1.00		4.0	3.9	3.7	4.4	4.0	4.9
2.00	5.0						
6.00						4.4	
Following A.M.	4.0	3.7	3.1	3.8	4.3	2.7	4.7
Phosphorus clearance, cc. plasma per hr.							
7–8	317	135	326	470	417	635	<3.5
8–9	172	188	310	610	488	710	<3.5
9–10	236	300	230	700	431	930	<3.5
	Parathormone 40 u. i.v.						
10–11	808	1400	1330	1055	980	2500	208
11–12	1030	1725	1320	1580	670	2800	1220
12–1	837	1825	2315	1360	670	2500	1250

* Lost.

† Experiment No. 3 upon this subject. Experiments 1 and 2 shown in table 6.

rate of excretion of phosphorus in the urine in this patient with hypoparathyroidism two hours after the parathormone injection, in spite of the low rate in the control periods, was well within the range found

for the normal individuals two hours after a similar injection of parathormone. This relatively enormous rise in hourly rate of excretion, in the extreme instance from 1.7 to 83.5 mgm. per hour (table 5), showed most strikingly the effect of parathormone on the excretion of phosphorus in the urine in the hypoparathyroid patient.

TABLE 2

Intravenous parathormone

Helen C. Hypoparathyroidism

EXPERIMENT I						EXPERIMENT II					
Urine			Serum, mgm. per cent			Urine			Serum, mgm. per cent		
Time	Vol., cc.	P/hr., mgm.	Time	P	Ca	Time	Vol., cc.	P/hr. mgm.	Time	P	Ca
7–8 A.M.	98	<0.2	10 A.M.	5.8		7–8 A.M.	475	1.8			
8–9 A.M.	125	<0.2	10.25	5.7	7.6	8–9 A.M.	165	1.0			
9–10 A.M.	107	<0.2				9–10 A.M.	100	1.2			
Parathormone 40 u. i.v. (10.05 A.M.)						10–11 A.M.	100	1.7	11 A.M.	5.6	6.9
10–11 A.M.	112	6.5	11.00	5.3	7.6	Parathormone 40 cc. i.v. (11.25 A.M.)					
11–12 A.M.	120	34.0	11.50	5.4	8.4	11–12 A.M.	90	25.8	12.30 P.M.	5.1	6.7
10–1 P.M.	29	15.1	1.25	5.4	8.4	12–1 P.M.	112	83.5			
1–2 P.M.	26	6.9				1–2 P.M.	45	41.5	1.30 P.M.	5.3	6.9
2–3 P.M.	33	7.2	3.10	5.4	8.0	2–3 P.M.	40	25.9			
						3–4 P.M.	95	20.0			
									4.20 P.M.	5.2	6.7

Plasma inorganic phosphorus

Considering the large amounts of phosphorus poured out in the urine after the injection of parathormone, one might anticipate a fall in the inorganic phosphorus of the plasma, as had been previously noted (1) (2). There was observed, with one exception (Robt. C., table 1), some lowering of the inorganic phosphorus of the plasma. This was not very marked, however, even after three hours of increased phosphorus excretion. Twenty-four hours after the injection, the inorganic phosphorus of the plasma was, as a rule, lower than in the control sample. In two instances (Henry C. and F. F., table 1) the 24-hour inorganic phosphorus of the plasma was very much lower than the control value.

Serum calcium

In view of the interrelationship of the metabolism of calcium and phosphorus and of the well-known effect of parathormone in producing an elevation of the calcium of serum, considerable interest attaches itself to the observations on the calcium of serum made here. In four of the normal subjects the calcium of the serum fell (table 3). In one instance (Henry C., table 3) a rise of 0.8 mgm. in 24 hours was observed. In the patient with hypoparathyroidism a rise in calcium

TABLE 3

Serum calcium

TIME	SUBJECTS—NORMAL					HYPOPARATHYROID
	Henry C.	James R.	Sam W.	Thomas S.	F. F.	Helen C.*
9.00 A.M.	10.6	11.2		10.5		6.3
10.00			10.6		10.3	
	Parathormone 40 u. i.v.					
11.00	10.4					6.2
12.00	10.3					6.7
1.00 P.M.			9.9	10.4	10.3	
2.00	10.1					
3.00						6.5
4.00						
5.00						
6.00					9.5	
Following A.M.	11.2	10.0	9.9	9.7	9.4	6.1

* Experiment no. 3 upon this subject. Experiments 1 and 2 shown in table 6.

of the serum occurred during the first experiment; no change took place during the second, and a rise at two and at five hours, followed by a return to the control level at twenty-four hours, was observed during the third experiment.

Fluid intake and output

In order to study the nature of the observed outpouring of phosphorus in the urine, and also because of the fact that parathormone has been used as a diuretic, observations upon urine volume were made. The diuretic effect of parathormone (table 4) was inconstant.

In three of the normal individuals there was a definite increase in urine volume. In the remaining subjects no diuresis but rather the reverse was observed. The absolute amount of water intake whether 200 cc. or 100 cc. per hour did not seem to influence this. A possible explanation for the variation in diuretic effect of parathormone may lie in the fact that the water given to these subjects each hour was itself a diuretic. The parathormone would then have been a second diuretic and some variation in its effect might have been expected.

TABLE 4

Water intake and urine volume in cubic centimeters

TIME	SUBJECTS—NORMAL												HYPOPARATHYROIDISM	
	Henry C.		Robt. C.		J. R.		S. W.		T. S.		F. F.		Helen C.	
	Intake	Urine volume	Intake	Urine volume	Intake	Urine volume	Intake	Urine volume	Intake	Urine volume	Intake	Urine volume	Intake	Urine volume
7–8	200	75	200	74	200	96	200	165	100	250	100	130	100	165
8–9	100	43	200	90	200	110	200	248	100	125	100	212	100	100
9–10	100	73	200	100	200	82	200	254	100	132	100	159	100	100
Three hr. total u.		191		264		288		667		507		501		365
	Parathormone 40 units i.v.													
10–11	100	167	200	136	200	258	200	256	100	275	100	163	100	90
11–12	100	135	200	195	200	137	200	262	100	*	100	68	100	112
12–1	100	102	200	240	200	150	200	157	100	90	100	55	100	45
Three hr. total u.		404		571		545		675		365		286		247

* Lost.

Calcium in urine

It had been demonstrated previously (1) (2) that no increase in the urinary excretion of calcium took place during the first few hours after parathormone administration. Observations upon the calcium excretion in the urine were repeated in two of the present experiments. Again, there was no increase in the urinary excretion of calcium (table 8).

Urine chlorides

It seemed quite possible that parathormone might cause an increased excretion of other anions besides phosphate. Of the other anions, the chloride was selected for study. Observations were made in three subjects (table 5). During the first hour after parathormone there was no striking change, but in the second and third hours a definite decrease in chloride excretion occurred. The excretion of chloride not only did not run parallel with that of phosphate but actually changed in the opposite direction.

TABLE 5

Urine chlorides, mgm. per hr.

TIME	SUBJECTS		
	Robt. C.	James R.	Sam W.
8–9	988	752	446
9–10	1084	557	660
	Parathormone 40 u. i.v.		
10–11	1107	877	457
11–12	663	395	314
12–1	624	363	248

Urea clearance

It was thought that the urea clearance, now so much used as an index of renal function, might be worthy of study. However, in the three observations made (table 6) no significant change appeared in the urea clearance during three hours after parathormone.

The urine pH

In view of large amounts of phosphate buffer excreted in the urine after parathormone, estimations of the pH were made in three individuals. No attempt was made to prevent the escape of CO_2 from the urine collected. The pH estimations were made promptly, a quinhydrone electrode being used. There was a definite tendency for the pH to shift (table 7) toward the alkaline side, particularly in the first two hours after the injection of parathormone. In the third hour after injection the pH shifted back toward the more acid range.

TABLE 6

Urea clearances

TIME	SUBJECTS		
	Robt. C.	James R.	Sam W.
8–9	62% NS	84% NS	66% MS
9–10	65% NS	87% NS	78% MS
	Parathormone 40 u. i.v.		
10–11	64% MS	86% MS	56% MS
11–12	76% MS	80% MS	68% MS
12–1	68% MS	130% MS	31% MS

NS = normal standard clearance.
MS = normal maximum clearance.

TABLE 7

*Urine pH**

TIME	SUBJECTS			
	Robt. C.	G. R.	Thomas S.	F. F.
7–8	5.9	6.4	6.7	7.2
8–9	6.1	5.7	6.2	7.2
9–10	6.0	5.7	7.1	7.5
	Parathormone 40 u. i.v.			
10–11	6.7	7.2	7.5	7.7
11–12	6.7	7.6	6.5	7.8
12–1	6.2	7.3	6.5	7.6

* No provision made to prevent escape of CO_2.

TABLE 8

Calcium in urine

TIME	TOTAL, MGM.	
	F. F.	Sam. W.
7–8	7.7	1.8
8–9	5.8	1.4
9–10	6.2	1.9
	Parathormone 40 u. i.v.	
10–11	3.6	1.4
11–12	1.9	1.2
12–1	6.7	1.5

DISCUSSION

Following the intravenous injection of parathormone there was observed an immediate and striking outpouring of phosphorus in the urine. This occurred quite regularly both in normal individuals and in a patient with hypoparathyroidism. In the latter patient, who had been kept on a low phosphorus diet and who consequently had a minimal excretion of phosphorus in the hours of control observation, the relative increase in excretion of phosphorus was greater than in the normal individuals. The amount of phosphorus eliminated in the urine was independent of the urine volume. In some instances following parathormone there was a moderate diuresis associated with a marked increase in phosphorus excretion; in other instances, the urine volume in the hours after parathormone was decreased while the amount of phosphorus eliminated was very much increased. The increased excretion of phosphorus was, therefore, not merely part of a general diuresis.

The observation that the excretion of chlorides was decreased when the phosphorus was increased showed that parathormone did not affect all anions in a similar manner. One would like to have information about the carbonate and possibly the sulphate ions. However, the fact that the excretion of the chloride anion is unaffected by the injections of parathormone, or at least is affected differently, suggests that parathormone acts in a specific manner towards phosphate, at least as far as anions are concerned.

The absence of alteration in urea clearance in the hours following the injection of parathormone indicates that the function of the kidney as measured by that test was not altered by the injection. The apparent alteration in urine pH may be significant, but at present is without explanation.

With regard to the mechanism of the increase in urinary phosphorus excretion three possibilities are suggested.

(1) Phosphate might be poured into the blood and subsequently be excreted in larger amounts in the urine. If this were the explanation, one would expect to find, shortly after the injection of parathormone, a rise in the inorganic phosphorus of the plasma. This was not observed in any case. On the contrary, as a rule, some fall of inorganic phosphorus was found.

(2) Non-diffusible phosphate in the plasma might be rendered diffusible. The suggestion that urinary phosphorus may be derived either wholly or in part from the acid-soluble organic phosphorus of the blood was made by Eichholtz, Robison and Brull (9). On the other hand, Brain, Kay and Marshall (10) found that the organic acid-soluble phosphorus of the blood was not a direct source of urinary phosphorus. In any case, the organic acid-soluble phosphorus of the plasma is almost wholly inorganic. The inorganic phosphorus of the plasma of normal individuals has been shown by Grollman to be completely ultrafiltrable (7). Moreover, even the high inorganic phosphorus concentration of the plasma in patients with hypoparathyroidism was found by one of us to be entirely ultrafiltrable (2). So far no form of non-diffusible phosphorus has been demonstrated in the plasma in sufficient amount to account for the increased loss of phosphorus in the urine by its conversion into a diffusible form.

(3) The excretion of phosphorus by the kidney might be primarily increased in one of three ways: (*a*) increased filtration of phosphate through the glomeruli, (*b*) excretion through the tubules, (*c*) decreased reabsorption of phosphate from the tubules. With reference to *a*, *b* and *c*, one of which would seem to offer the most likely explanation for the observed loss of phosphorus in the urine after parathormone injection, we have attempted to obtain data which would point to one. So far the results obtained have not been sufficiently reliable to lead to any conclusion.

In 1932 Thomson and Pugsley (11) reported that in dogs the intravenous injection of 200 units of parathormone resulted in a rise of the calcium of the serum without a fall in inorganic phosphorus. They did not report any observations of the inorganic phosphate in the urine. Thomson and Pugsley concluded that, since there was no fall in inorganic phosphorus preceding the rise of calcium in the serum, the hypothesis suggested by Albright and Ellsworth (1) to explain the mechanism of action of the parathyroid hormone was untenable. In the present experiments, however, it was found that even when large amounts of phosphorus were lost in the urine, the change in the inorganic phosphorus of the plasma might be relatively slight. The absence of a pronounced fall in the inorganic phosphorus level of the plasma, therefore, is not evidence that there has not been a marked loss of inorganic phosphorus in the urine.

From the observation of marked loss of phosphorus in the urine with comparatively slight change in the level of inorganic phosphorus in the blood, it is apparent that there was a very rapid mobilization of inorganic phosphorus from the tissues into the plasma. There are several possible sources for this phosphorus. The organic acid-soluble phosphorus of the corpuscles, the phosphorus of muscle, the phosphorus of intercellular fluids, the phosphorus of bone, are perhaps the most probable sources of origin. Determinations of small changes which might occur in muscle phosphorus or in the phosphorus of intracellular fluids after parathormone are not at present feasible. On the other hand, the acid-soluble phosphorus of the corpuscles has been studied in certain conditions associated with an increased excretion of phosphorus in the urine. Ammonium chloride and carbon dioxide acidosis produce phosphaturia, and after a time a lowering of plasma inorganic phosphorus (8). Ammonium chloride acidosis was shown to be accompanied by a marked fall in the organic acid-soluble fraction of the blood (8). It is possible that the same store of phosphorus may have been called upon during the increased phosphorus excretion following parathormone. The acid-soluble phosphorus of the blood is at present being investigated as a possible source of the phosphorus lost in urine. The low concentrations of inorganic phosphate in the plasma twenty-four hours after the injection of parathormone observed in two instances (table 1) suggests that the stores of phosphorus called upon to supply the phosphorus lost in the urine may be replaced temporarily at the expense of the inorganic phosphate of the plasma.

The bones, of course, constitute a large and readily available storehouse of both phosphorus and calcium. In the present experiments the absence of a rise in the calcium of the serum in five experiments, together with the fact that there was no increased excretion of calcium in the urine, indicates that in those instances the bones were not called upon to supply phosphorus.

The fall of calcium of the serum observed in some of these experiments seems at first to be contrary to the general experience with parathormone injections. In the dog, single injections produce a rise of calcium which is sufficiently regular to permit the use of that animal for purposes of biological assay, provided a number of dogs are used.

In the normal human subject, however, single injections of parathormone may not produce a rise of serum calcium. Certainly the dose employed here, of moderate size and given intravenously, did not in several experiments result in the elevation of calcium of the serum, which is generally supposed to be the end-result of parathyroid administration.

Since the single injections of parathormone studied here in many instances produced no rise in the calcium of the serum, and since some source other than the bones appears to have supplied the phosphorus lost, the suggestion might be made that, when multiple injections of parathormone are employed, the bones as well as other phosphorus stores are called upon, with the result that the calcium is elevated in the serum.

In any case, the regularity of the increased elimination of phosphorus in the urine after parathormone in the absence of any elevation of the calcium of the serum suggests very strongly the fundamental nature of the effect of parathormone upon phosphorus metabolism.

SUMMARY

1. Following the intravenous injection of 40 units of parathormone in normal individuals there was an immediate outpouring of phosphorus in the urine.

2. There was in some instances a diuresis, but in others this did not occur.

3. The urea clearance was not markedly altered, the chloride excretion was diminished rather than augmented, the pH of the urine tended to shift to a more alkaline range.

4. There was a relatively slight fall in plasma inorganic phosphorus.

5. The serum calcium in several instances, instead of rising, tended to fall.

6. The theoretical implications of these findings are briefly discussed.

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CALCIUM AND PHOSPHORUS STUDIES

X. The Effect of Variation of Calcium, Phosphorus, and of Vitamin D in Diet on Iron Retention in Rats[1]

DAVID H. SHELLING and HUGH W. JOSEPHS

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In the course of some experiments in which rats were fed diets composed of dried powdered milk and varying amounts of calcium and phosphorus, it was noted that the animals receiving a ration which was high in calcium and low in phosphorus became extremely anaemic, whereas those receiving a diet which was low in calcium and high in phosphorus became only moderately anaemic. The experiment was then repeated on small groups of animals, with the aim of determining the retention of iron on diets (1) high in calcium and low in phosphorus, (2) high in phosphorus and low in calcium, and (3) optimal in calcium and phosphorus. In order to keep the phosphorus intake at a low level, the amount of milk had to be restricted, so that the protein intake was necessarily below optimal levels. The amount, however, was equal in all three diets, so that whatever effect was obtained could not have been due directly to the low intake of protein. The composition of the diets is given in table I.

In the first series, six animals were used in each group. They were fed the respective diets, beginning from the age of 21 days. At the end of 10, 25, and 40 days, respectively, 2 animals from each group were killed, and the haemoglobin in the heart's blood was determined by the Newcomer method. Each animal was then dried to constant weight and ground up in a mortar. Portions of the animal were ashed and the iron content of the entire animal was determined according to the method previously described by one of us.[2] Since the iron content

[1] Aided by the John Howland Memorial Fund.

[2] Josephs, H. W., *J. Biol. Chem.*, *96*, 559 (1932).

of rats at 25 days had been previously determined on a control series,[2] it was possible to calculate the amount of iron retained by each rat during the course of the experiment. The results are given in table II.

In the second series, two groups of four rats each were fed the high calcium and low calcium diets, respectively, to which was added 1.0 per cent of viosterol 1-D, in order to ascertain the effect of vitamin D on iron retention. Two animals from each group were killed at 20 and 40 days, respectively, and the determinations carried out as in the

TABLE I

Composition of diets

	HIGH Ca-LOW P	HIGH P-LOW Ca	OPTIMAL Ca AND P
Whole powdered milk	30.0	30.0	30.0
NaCl	0.5	0.5	0.5
KCl	0.5	0.5	0.5
$CaCO_3$	2.5		0.6
Na_2HPO_4 (anhyd.)		3.0	1.4
Butter	4.0	4.0	4.0
Lactose	30.5	30.0	33.0
Glucose	32.0	32.0	32.0
	100.0	100.0	100.0
Wheat germ extract equal to	10%	10%	10%
	Ca = 1.270 gm. % P = 0.195 gm. % Ca:P = 6.5:1	Ca = 0.270 gm. % P = 0.850 gm. %. Ca:P = 0.3:1	Ca = 0.510 gm. % P = 0.500 gm. % Ca:P = 1:1

first series. The results are shown in table III. For comparison, the figures for total iron content of rats on a diet of certified milk alone are also included. These figures were taken from a previous experiment, published elsewhere.[2]

Of course, these various series of animals are not strictly comparable. Firstly, litters were mixed and the rats of the second series belonged to different litters from those of the first; secondly, the age at which the animals were placed on the diets differed in the two series; and thirdly, the diet of milk alone, used for comparison, was entirely different in composition from the diet used in the present experiments, being,

TABLE II

Effect of variation of calcium and phosphorus in the diet on iron retention

	NUMBER	AGE STARTED ON DIET	EXPERIMENTAL PERIOD	WEIGHT	HAEMOGLOBIN PER CENT	TOTAL IRON	GAIN IN IRON FROM START
		days	*days*	*grams*	*grams*	*mgm.*	*mgm.*
		21	0			0.75	
	3953	21	10	35	9.1	0.83	0.08
	3955	21	10	40	8.4	1.15	0.40
High P-low Ca	3954	21	25	55	11.4	1.95	1.20
	3956	21	25	45	11.1	1.48	0.73
	3957	21	40	64	12.6	2.05	1.30
	3958	Died					
	3961	26	10	53	14.7	1.65	0.90
	3962	26	10	44	12.6		
Ca:P = 1:1	3959	26	40	100	9.0	2.25	1.50
	3960	26	40	97	10.2	2.65	1.90
	3947	21	10	45	7.8	0.80	0.05
	3948	21	10	45	7.9	0.85	0.10
	3949	21	25	59	7.7	1.35	0.60
High Ca-low P	3950	21	25	61	7.6	1.30	0.55
	3951	21	40	60	8.6		
	3952	21	40	60	7.8	1.13	0.40
		21	0			0.75	
		21	10			1.05	0.30
Milk diet alone*		21	25			1.35	0.60
		21	40			1.45	0.70

* *Note:* The figures for iron content of rats on milk alone were taken from previous work. The iron content of dried milk is considerably higher than that of the certified milk as used in previous work. This fact probably explains the failure to develop any great degree of anaemia.

TABLE III

Effect of viosterol 1-D (1 per cent) on iron retention

	NUMBER	AGE STARTED ON DIET	EXPERIMENTAL PERIOD	WEIGHT	HAEMOGLOBIN PER CENT	TOTAL IRON	GAIN IN IRON FROM START
		days	*days*	*grams*	*grams*	*mgm.*	*mgm.*
		26	0			0.90	
	3964	26	20	61	12.0	1.75	0.85
High P-low Ca	3965	26	20	62	14.1	1.98	1.08
	3963	26	40				
	3966	26	40	80	10.6	2.75	1.85
	3967	26	20	47	11.2	1.35	0.45
	3968	26	20	47	10.5	1.45	0.55
High Ca-low P	3969	26	40	50	9.5	1.10	0.20
	3970	26	40	50	10.6	1.50	0.60

among other things, much lower in iron content. The results, however, are sufficiently striking to be beyond the range of variation dependent on the lack of strict controls.

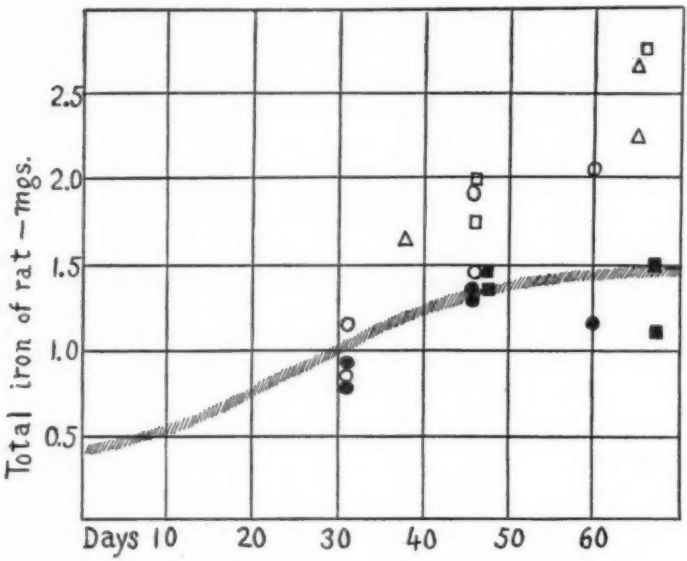

CHART 1. TOTAL IRON CONTENT OF RATS

Note: Hollow circles = High phosphorus—low calcium—no viosterol. Solid circles = Low phosphorus—high calcium—no viosterol. Triangles = Phosphorus and calcium equal—no viosterol. Hollow squares = High phosphorus —low calcium + viosterol. Solid squares = Low phosphorus—high calcium + viosterol.

The shaded line represents total iron content of rats on milk diet alone.

The results may be briefly summarized as follows:

(1) The haemoglobin is much lower in the rats fed the diet of high calcium and low phosphorus content than in those fed the other diets with and without viosterol.

(2) The iron retention is much lower in the animals fed the high calcium diets than in those on the other diets, and actually lower than in rats fed on certified milk of extremely low iron

content. This result was rather surprising, since, *a priori*, it would be expected that the high phosphate would cause either a more complete precipitation of iron in the intestine and thus interfere with absorption of iron or cause a greater excretion of iron in the large intestine along with the excess phosphate, and that an excess of calcium in the diet would tend to remedy such a loss of iron. Actually, the opposite has occurred. The exact mechanism by which the high calcium intake interferes with iron retention is not certain, but it is possible that the iron is carried down with the calcium-phosphate precipitate either before absorption has taken place or during the process of excretion.

(3) Viosterol, when added to the diet, seemed to increase the retention of iron in the rats fed the high-phosphorus diet, but it had no effect on the iron retention in those fed the high calcium diet. This result of giving viosterol is, however, no more than suggestive, because of the differences between the two series, as previously pointed out, and of the small number of animals.

No conclusions are to be drawn from this experiment, which is preliminary in nature. It is not possible to decide whether the haemoglobin failed to increase on the high calcium diet because the latter prevented the retention of iron, or whether the diet in some way interfered with haemoglobin formation, with the result that the unused iron was lost to the body. Further studies are now in progress.

CALCIUM AND PHOSPHORUS STUDIES

XI. Effect of Prophylactic and Curative Doses of Standardized Viosterol on Human Tissues: Necropsy Report of 13 Cases Showing no Tissue Damage

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The first reference to the effects of large doses of irradiated ergosterol on the animal organism was made by Rosenheim and Webster (1), in 1927. They found that 10,000 times the minimal antirachitic dose was not lethal to rats. However, shortly afterwards, Pfannenstiel (2) and Kreitmair and Moll (3) reported that "enormous" doses produced pathologic lesions in the soft tissues of a variety of species of animals—some being more susceptible than others. Their results were corroborated by numerous investigators, many of whom, like Pfannenstiel and Kreitmair and Moll, failed to state the antirachitic potency of the irradiated ergosterol used, except that it was given in so many milligram doses. In the experiments in which the dosages are stated, the range between the toxic and the therapeutic dose appears to be quite wide. Collazo, Rubino and Varela (4) found that rats died within six weeks when fed the McCollum rachitogenic diet and 50,000 times the therapeutic dose of irradiated ergosterol. Harris and Moore (5) and Light, Miller and Frey (6) observed that 100,000 times over-dosage was fatal to rats, whereas 10,000 times was not toxic even when fed for as long as six months. Similar results were obtained by Bills (7), Harris (8), Hoyle (9), Shelling (10), Jones (11), Duguid (12) and others, who, in addition, stressed the importance of the calcium and phosphorus of the diet as a factor in the toxicity of irradiated ergosterol.

In human beings, the margin of tolerance has not been definitely determined. In the earlier reports on the toxic effects produced in infants by irradiated ergosterol, the dosages are given in terms of

milligrams, instead of "rat" units, so that the exact antirachitic potency of these substances cannot be determined. With regard to *standardized* ergosterol, as produced in America, there are several reports from which it may be inferred that in human beings the toxic dose is also quite remote from the therapeutic level. Thus Hess, Poncher, Dale and Klein (13) gave as much as 40 times the therapeutic dose of viosterol to babies for six months, and noted no untoward results other than a tendency to constipation and colic. Reed and Seed (14) and Rappoport and Reed (15) gave 300 times the ordinary dose of viosterol to normal individuals and to patients afflicted with parathyroprivic tetany. In the latter, the tetany was alleviated and no toxic manifestations developed; but in some of the individuals with intact parathyroids, mild symptoms developed when the administration of viosterol was continued for several weeks. Crim and his associates (16) fed 150 times the usual dose of viosterol to normal and to tuberculous individuals subsisting on diets fairly rich in calcium and found no toxic manifestation, except very mild symptoms in a few patients subjected to the therapy for a relatively long time.

The lethal dose for human beings is also unknown. The known largest doses are those used by Reed (17) and Rappoport and Reed (15) in patients suffering from asthma and other ailments, and by Spies and Hanzal (18), in patients about to die of incurable maladies. The dose used by the former was calculated by Bills (19) as 920 times the ordinary therapeutic dose of irradiated ergosterol; and the amount used by the latter amounted to 6000 times the usual dose. Hypercalcemia developed in both instances, but symptoms of serious poisoning were not noted in Reed's patients, and pathologic calcification was not found when Spies and Hanzal's patients were examined *post mortem*.

It is of interest that the reports on the range between the therapeutic and toxic dose of the American made, *standardized*, irradiated ergosterol differ materially from those of the German product "Vigantol." In 1928 and 1929, several accounts of toxic effects from the use of "Vigantol" appeared in the clinical literature. These reports came mostly from Germany (20), but Hess and Lewis (21), in New York, also reported adverse effects from the use of this preparation. The potency of this substance, which was presumed to be vitamin D, was

then expressed in terms of *milligrams*, and dosages of about 1 to 5 milligrams were recommended for the healing of rickets; yet, when as little as 5 milligrams of Vigantol was given, some children reacted with a peculiar train of symptoms—anorexia, vomiting, diarrhea, hematuria; and in some instances the therapy is said to have caused death. According to Bills' (19) calculations, 5 milligrams of Vigantol could hardly supply enough *vitamin D* to account for the observed effects, since pure "calciferol" contains only 40,000 International antirachitic units per milligram, and the potency of 1 mg. of unpurified irradiated ergosterol in the form of Vigantol is probably only a fraction of that amount.

What then caused the toxic effect of Vigantol, and why are accounts of the toxicity of vitamin D in children no longer reported, in spite of the fact that irradiated ergosterol has been used, in some instances, in fairly large doses and for relatively long periods of time? In 1928 Dixon and Hoyle (22) and Underhill (23) suggested that the toxic action of Vigantol was due to the presence in it of a toxic by-product the result of the irradiation of the ergosterol in alcohol, as in the German method, instead of in oil, as in the English method. This possibility, however, was denied by Harris (24). In 1930, Holtz (25) and Windaus (26) also supposed that irradiation produced two distinct substances—vitamin D and a "calcifying" toxic material. In 1931, Göttche and Kellner (27) established the important point that the toxic and therapeutic doses of different irradiated ergosterols do not run parallel, and that with Vigantol the margin between the toxic and therapeutic dose was quite narrow. Like Dixon and Hoyle, they too suggested that the high toxicity of Vigantol was due to some technical difficulty, but they were unable to prove it. Bills (19), however, has recently proved definitely that the toxic substance in Vigantol is *toxisterol or Substance 248*, and not vitamin D or *calciferol*, and that it is a by-product of irradiation of ergosterol in alcohol, as first suggested by Dixon and Hoyle (22). The steps leading to this discovery are enumerated in a recent Review by Bills (19). In brief, when ergosterol is irradiated in alcohol, instead of in ether or oil, as is English or American ergosterol, toxisterol is formed in amounts out of proportion to the vitamin D it contains. Toxisterol shows an intense ultraviolet absorption band at 248 mμ, instead of at 285 mμ, as does pure calciferol,

and hence the designation "substance 248." Unfortunately, irradiation of ergosterol in alcohol was precisely the method used for the manufacture of Vigantol, which apparently was a mixture of toxisterol and vitamin D.

Notwithstanding the fact that Vigantol probably produced some toxic effects in human beings, it is equally true that many of the reports are groundless and the clinical and pathologic findings purporting to show its toxic effects are so slight and insignificant as to be in the realm of normal or that they have no etiologic relation to vitamin D. As with all new therapeutic discoveries, so with vitamin D: Its praises and condemnations run in cycles. For example, before the introduction of vitamin D, slight cellular infiltration of the wall of the kidney pelvis in a child suffering from chronic pyelitis, would be looked upon as a natural and expected finding; yet, as reports of toxicity of Vigantol were forthcoming, such or similar findings assumed significance in the eyes of investigators as to be thought worthy of record as signs of poisoning by vitamin D. Fortunately, authentic incidences of poisoning with therapeutic doses of *standardized* viosterol have not been reported, but, at the same time, there are also but few records of the effects of the use of therapeutic amounts of this substance on the tissues of human beings. The present report deals with such a study. It must be added that in our five years of experience with the use of *standardized* viosterol in fairly large doses in several hundred children, manifest symptoms of viosterol overdosage were never encountered, although the amounts given to some were from 5 to 10 times the ordinary therapeutic dose; and the duration of administration, in some instances, was more than two years. The children, whose tissues we had occasion to examine, received viosterol during life, and died of diseases not incident to therapy with viosterol. In none of these was there evidence of pathologic changes directly attributable to vitamin D therapy. The duration of therapy in these cases varied from a few weeks to more than a year. Two of the children received from 15 to 40 drops[1] of viosterol (250-D) daily for ten and twelve months, respectively. One of them received viosterol for the cure of rickets; the other suffered from advanced tuberculosis and rickets and was

[1] Twelve hundred to 3000 Steenbock or 3240 to 8100 International units.

given sodium phosphate along with viosterol, for a short time, in an attempt to induce calcification in the peribronchial glands. The remaining cases, grouped in table 1, received viosterol for shorter or longer periods; these, likewise, failed to show changes in the soft tissue which could be attributed to overdosage with viosterol. The bones of the entire group were studied radiographically and histologically, in order to ascertain the effects of viosterol on the healing of rickets in those showing active rickets shortly before death, and on the bones of those in whom the rickets had healed completely or had never been present. The histopathology of the bones will be discussed presently. The report of the two cases receiving large doses of viosterol for relatively long periods, follows:

Case 1. H. N., colored, male. First seen at the Harriet Lane Home dispensary at the age of eight months because of severe rickets. He was given 15 drops of viosterol daily and the rachitic process healed completely within four months. Because the child was very large and growing rather rapidly, and because the mother feared the recurrence of rickets, she continued the viosterol (20 drops daily) for an additional six months. The calcium and inorganic phosphorus concentrations at the end of this period were 12.0 and 5.5 milligrams per cent, respectively. Soon after viosterol therapy was discontinued, the child was admitted to the hospital with meningococcus meningitis from which he succumbed within a few days. The findings at autopsy may be summarized as follows: "Every organ appears normal except the brain." In the brain "there is diffuse purulent meningitis more marked over the right side of the brain and over the base. The exudate seems to be along the vessels but the vessels appear quite normal in the center of the exudate on each side."

X-ray of bones: Bright terminal line; shaft normal (fig. 1, *B*).

Histology of bones: The cartilage appears normal. The calcification is heavy and the lattice of calcified matrix, bordering on the cartilage, is thick. The shaft looks normal. New bone formation is actively in progress and the osteoid borders are as wide as those seen in normal bone. Destructive processes are going hand in hand with new growth. The marrow appears normal (fig. 1, *A*). *Summary:* Normal bone. The lime salt deposit in the cartilage and the subjacent lattice are perhaps slightly heavier than normal.

Case 2. L. C., colored, male, admitted to the Harriet Lane Home at the age of five months because of convulsions. He was found to have a hypocalcemia, active rickets, latent tetany, undernutrition and physical and x-ray signs of disseminated pulmonary tuberculosis (miliary ?). He was given $CaCl_2$ and increasing doses of viosterol, up to 40 drops daily, for a short time; the serum calcium rose to normal values and the tetany disappeared. He was continued on 40 drops of viosterol

daily and the rachitic process healed quite well. About one month after admission he was given, in addition to a well-balanced diet and viosterol, 3.0 gm. of anhydrous Na_2HPO_4 daily (P = 0.654 gm.) for a period of five weeks. This was done in an attempt to induce calcification in the tuberculous peribronchial glands, since it was previously found that diets high in phosphorus and optimal in calcium predispose to calcification by vitamin D (4). The patient tolerated the sodium phosphate quite well and, in spite of the activity of his pulmonary lesions, he did not lose weight. He was discharged from the hospital, and viosterol and milk were

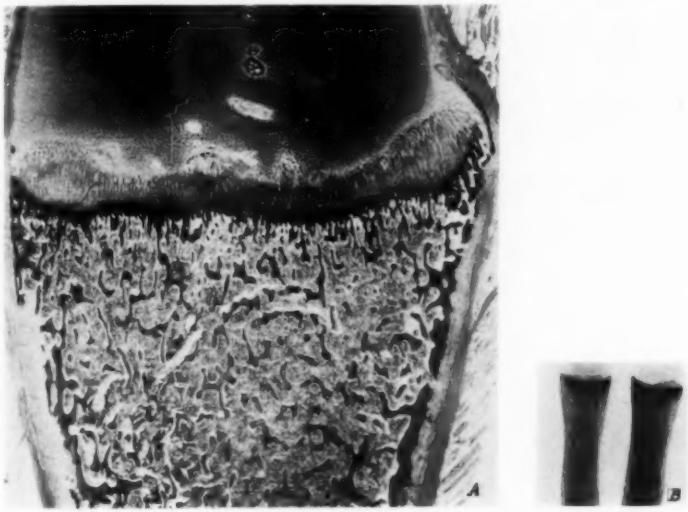

FIG. 1. (*A*) HISTOLOGIC AND (*B*) X-RAY APPEARANCE OF RIB IN CASE 1 (H. N.), AN EIGHTEEN-MONTH-OLD COLORED CHILD WHO HAD PREVIOUSLY HAD RICKETS AND HAD RECEIVED VIOSTEROL FOR TEN MONTHS

Note the heavy calcification in the cartilage and the thickness of the lattice bordering on the cartilage. Histologically a normal, well calcified bone.

furnished to him through the aid and under the supervision of the social service department. He was followed clinically through frequent visits to the dispensary where the chest and the long bones were radiographed and blood was taken for calcium and inorganic phosphorus determinations. X-ray films of the chest showed that there was some improvement in the tuberculous process and also that there was evidence of calcification of the peribronchial glands. Some of the later x-ray films of the long bones showed that all vestiges of rickets had disappeared and that the ends of the long bones were well calcified. There was no hypercal-

cemia or other manifestations of viosterol overdosage, the highest value for calcium in the serum being 9.9 milligrams per cent. His general condition, however, was poor and he did not gain much in weight.

About 11 months after the first admission he was readmitted to the hospital because of failure to gain, cough and general debility. He died shortly afterwards, at the age of 18 months, and after being, most of the time, on 30 or 40 drops of

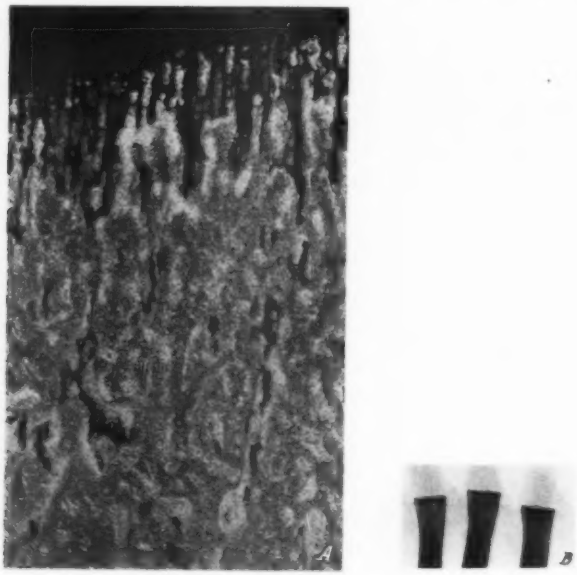

FIG. 2. L. C., CASE 2

Note brightness of terminal zones in the x-ray film (*B*) and the somewhat heavy deposition of lime salts in the cartilage and the somewhat longer and thicker trabeculae. (*A*) A good example of a normally well calcified bone.

viosterol daily for twelve months. An autopsy was performed. A summary of the pathologic findings follows:

Liver: Weighed 280 grams. Smooth capsule which showed a number of small fibrous thickenings in the peritoneal coat. On section the lobulations are quite distinct. Very few calcified tubercles are scattered about. The bile ducts and gall bladder are normal.

Spleen: Normal.

Lungs: Left pleural cavity normal. There are a few old fibrous adhesions between the lobes of the right lung and between the surfaces of the lung and pleura.

The left lung is air-containing throughout. In several places there are old areas which contain much scar tissue and very *small calcified tubercles*. They have the appearance of being *completely healed*. The largest of such areas is seen at the medial margin of the lower lobe. It has the appearance of a group of small healed tubercles, rather than that of a primary lesion. The lower lobe of the right lung contains a number of similar tubercles and groups of tubercles. The upper lobe of the right lung is extensively involved in an old tuberculous process, the course of which is now impossible to decipher. There is a great deal of scarring of the lung substance and there are a few old hyaline and *calcified* tubercles scattered about, all of these being very small. No primary lesion is found in the lung. Around the trachea there are a number of lymph nodes which are filled with large caseous masses. These too have the appearance of being very old and well healed, as they are all surrounded by connective tissue capsules. They also appear to contain some gritty *calcified* substance.

The blood vessels, kidneys, ureters, pancreas, testes and bronchi all appear normal.

X-ray of bones: Rickets absent; terminal zone bright (fig. 2, *B*).

Histology of the bones: (Section of rib). The condition of the cartilage shaft junction, as seen in the histologic preparations, is a beautiful example of the normal. The calcification in the cartilage appears unusually heavy, and the trabeculae of the calcified cartilaginous substance, with their actively forming investments of bone, seem longer and somewhat thicker than usual (fig. 2, *A*).

COMMENT

There is nothing of note about the first case, except that abnormal calcification was not discovered in any of the tissues of the body, in spite of the fact that three to four times the prophylactic dose of viosterol had been given for a period of ten months. In the second case, the viosterol and sodium phosphate were given with a view of producing calcification in the tuberculous process in the lung; and this was partly accomplished, as is evidenced by the presence of calcified tubercles and peribronchial glands in this eighteen months old child. However, lime salt deposition occurred *only* in the caseous tuberculous tissue and in the bones, but nowhere else in the body. Examination of the tissues of the remainder of the group also failed to show evidence of toxicity.

Effect of viosterol on the bones

Several observers have erroneously assumed that the transverse lines or dense ends, seen in the x-ray films of the bones of children

treated with vitamin D preparations, indicate a form of hypervitaminosis D, although none of these children presented clinical or chemical evidence of over-dosage. Göttche and Kellner (28) have recently reviewed these reports and concluded that the lines described as indicative of vitamin D toxicity were due, in most instances, to temporary retardation of growth as a result of intercurrent ailments, *i.e.*, "growth lines," and, in other cases, to the administration of elementary phosphorus along with vitamin D. The bones showing rather dense ends, they believe to be an expression of superior calcification rather than of toxicity.

The significance of transverse lines in the shafts of the bones has been investigated by Asada (29), Harris (30) and Eliot, Souther and Park (31). According to these observers, transverse lines are exceedingly common in children and even in adults, and they are merely manifestations of sudden arrest of growth resulting from chronic ailments or derangements in nutrition and are not the result of modern anti-rachitic therapy, since such "transverse lines" have been detected radiographically, by Moodie (32) and Elliot Smith (33) in the bones of Egyptian and Peruvian mummies.

The effect of elementary phosphorus on development of the osseous tissue was first studied by Wegner (34) and later by Kasowitz (35) and others; and although Kasowitz supposed that elementary phosphorus cured rickets, modern investigators disproved this notion and demonstrated that it produces sclerosis of the growing bone, which appears in the x-ray films as dense shadows, rather than healing in the provisional zone of cartilage. In some of the cases reviewed by Göttche and Kellner, vitamin D was given along with elementary phosphorus, and the dense ends of the bones observed in the x-ray films have been erroneously ascribed to over-dosage with vitamin D. Thus, for example, the changes in the bones in the case observed by Opitz (36) were due to the feeding of elementary phosphorus rather than to over-dosage with vitamin D, since his patient received elementary phosphorus in cod liver oil, in addition to 9 drops of Vigantol daily, and 18 exposures to the ultraviolet lamp.

Göttche and Kellner consider the dense ends of the bones of children receiving vitamin D regularly as an expression of superior calcification rather than an indication of toxicity by vitamin D. They call atten-

tion to the fact that the x-ray films of the ends of the bones of patients, reported to be over-treated with irradiated ergosterol, resemble those of Looser's cases of spontaneously healed "late rickets" and those of rachitic children treated with cod liver oil or sunlight. Hess (37) found that hypermineralization of the ends of bones is quite common among the children of Panama, since they are constantly exposed to intense sunshine; and it is probably also common in apparently normal children in other climes.

It is rather surprising that, in spite of the many clinical reports on the supposedly ill effects of irradiated ergosterol on the bones, there are no histologic studies of the bones of such cases and but few recorded histologic examinations of the bones of children to whom irradiated ergosterol was given over long periods but who showed no ill effects. Strauss (38) studied the organs of a rachitic child who had received about 100 milligrams of irradiated ergosterol over a period of two and a half months *ante mortem*, and found no histologic evidence of toxicity in the soft tissues or in the skeleton. The bones showed advanced but as yet incomplete healing of the rachitic process. The provisional zone of cartilage and the osseous trabeculae were well calcified, but part of the metaphysis, between the provisional zone and the diaphysis, was still free of lime salts. In short, the healing process did not differ from that brought about by cod liver oil or ultra-violet light. In the tissues of the thirteen children reported here, we too found no histologic evidence of toxicity by vitamin D in any of the organs examined, including the bones. The results of the histologic examination of the osseous tissue are tabulated in the accompanying table. The cases are arranged in the following order: Group I, children with active rickets to whom viosterol was administered as a therapeutic measure and in whom the x-ray films of the extremities showed that rickets was in process of healing or that it had healed completely some months before the viosterol was discontinued; Group II, children who received viosterol as a prophylactic against rickets. In Group I are included cases 1 and 2 already described, and also case 3. The former two received fairly large doses of viosterol for ten and twelve months, respectively, and the histology of the bones showed that all traces of rickets had disappeared, that the calcification of the trabeculae was normal and the growing ends had assumed a

TABLE I

Analysis of data on thirteen subjects who had received viosterol during life, either as a curative or a preventative measure against rickets, and whose tissues had been studied histologically

CASE NO.	NAME	COLOR AND SEX	AGE	RICKETS	C.L.O.	VIOSTEROL	DURATION	SYPHILIS	THERAPY	X-RAY DIAGNOSIS AND COMMENT	HISTOLOGY OF BONES	CAUSE OF DEATH (CLINICAL AND AUTOPSY)
						drops						
1	H. N.	C. M.	18 mos.	++++	0	15 20	4 mos. 6 mos.	0	0	Bright terminal line. Shaft normal	Normal bone. The salt deposition in the cartilage and the adjacent lattice are perhaps slightly heavier than normal	Meningococcus meningitis. *Autopsy:* every organ normal except brain, showing purulent meningitis over right side and over base
2	L. C.	C. M.	18 mos.	++++ Tetany	0	20 30 40 30 20	11 days 3 days 5 mos. 6 mos. 1 wk.	0	0	Rickets absent. Terminal zone bright. Transverse "growth lines"	Beautiful example of normal bone. Calcification in cartilage appears unusually heavy, and the trabeculae of the calcified cartilaginous substance with their actively forming investments seem longer and somewhat thicker than usual (fig. 2a)	Tuberculosis (pulmonary). Lipoid pneumonia. *Autopsy:* See text
3	F. U.	C. F.	14 mos.	++++	0	40	2 mos.	0	0	Marked rickets. Healing		Pulmonary tuberculosis. Tuberculosis meningitis. Rickets, healing
4	J. M.	C. M.	2 yrs.	+ −	12 cc.—1 mo.	50	1 mo.	0	0	Rickets absent. Dense terminal zone	Rickets was probably present as evidenced by the presence of some uncalcified osteoid beneath the cartilaginous zone. The provisional zone, however, is well calcified and there is no osteoid tissue in the trabeculae of the shaft	Generalized tuberculosis

5	D. C.	C. M.	14½ mos.	0	0	5	13½ mos.	0	0	Normal appearing ends and shaft	Not done	Pertussis, pertussis pneumonia. Pertussis encephalitis
6	W. L.	C. M.	7 mos.	0	0	15 25	2 mos. 4 mos.	++++	Salvarsan 6 × 7 × mercury 1/28/31 to 3/9/31	No rickets. Terminal zone snowy and dense-looking, but thin. All evidence of bone rickets disappeared	Completely calcified bone, undergoing rarefaction without evidence of new bone formation. Rarefaction probably due to terminal illness. Child treated for syphilis and dense zone may be due to anti-luetic and to viosterol therapy	Pertussis, pneumonia
7	J. C.	W. F.	10 mos.	0	½ teasp.—2½ mos. 10 cc.—5 days 16 cc.—3 wks.	20	5 mos.	0	0	No rickets. Rather bright ending of shaft, otherwise nothing special	Normal appearing, actively growing bone	Unexplained convulsions for 6 mos., refractory to therapy. Died in convulsion. *Autopsy:* No lesions found
8	C. C.	C. M.	4 mos.	0	0	20 10	6 wks. 9 wks. — 15 wks.	0	0	No rickets. Cortex and ends of bones well calcified. Transverse "growth line" in radii	Essentially normal appearing bone. New bone formation and old bone destruction are actively in progress	*Autopsy:* Congenital malformation of lung, heart, rectum and bladder
9	M. G.	C F.	3½ mos.	0	0	15 25	87 days 11 days — 98 days	0	0	No rickets	Line of ossification narrow. Costochondral junctions are a little swollen but have not the irregularities of rickets	Prematurity. Pneumonia. Septicemia. Hemorrhagic purulent pleurisy
10	G. B.	C. F.	3 mos.	0	0	15 20 15 20 10	35 days 3 days 4 days 29 days 14 days — 85 days	++++	Salvarsan 4 × mercury 12/28/30 –1/22/31	Except for fine network of transverse trabeculation with band-like effect at ends of bones, shafts appear normal	Except for evidence of pre-existing syphilis, not a trace of rickets is present	Prematurity. Congenital lues. Pneumonia. Acute nutritional disturbance

TABLE I—*Concluded*

CASE NO.	NAME	COLOR AND SEX	AGE	RICKETS	C.L.O.	VIOSTEROL	DURATION	SYPHILIS	THERAPY	X-RAY DIAGNOSIS AND COMMENT	HISTOLOGY OF BONES	CAUSE OF DEATH (CLINICAL AND AUTOPSY)
						drops						
11	R. M.	C. F.	23 mos.	0	0	40	51 days	0	0	No rickets	No evidence of rickets	Miliary tuberculosis. Tuberculous meningitis
12	D. S.	C. F.	10 wks.	0	0	15	33 days	+++	0	No rickets. Radii show transverse lines; ribs show bands, separated by a zone of rarefaction from shaft proper	See text	Prematurity. Congenital syphilis. Pneumonia. Malformation of urinary tract
13	F. H.	W. F.	4½ mos.	0	0	20	23 days	++++	Salvarsan 2 ×	No rickets. Ends of shafts brightly delineated	Trabeculae of shaft appear normal. Both new bone formation and destruction of old bone are present. Some remains of syphilitic involvement of cortex. Marrow is normal	Congenital syphilis. Lipoid-cell pneumonia. Pneumococcus meningitis

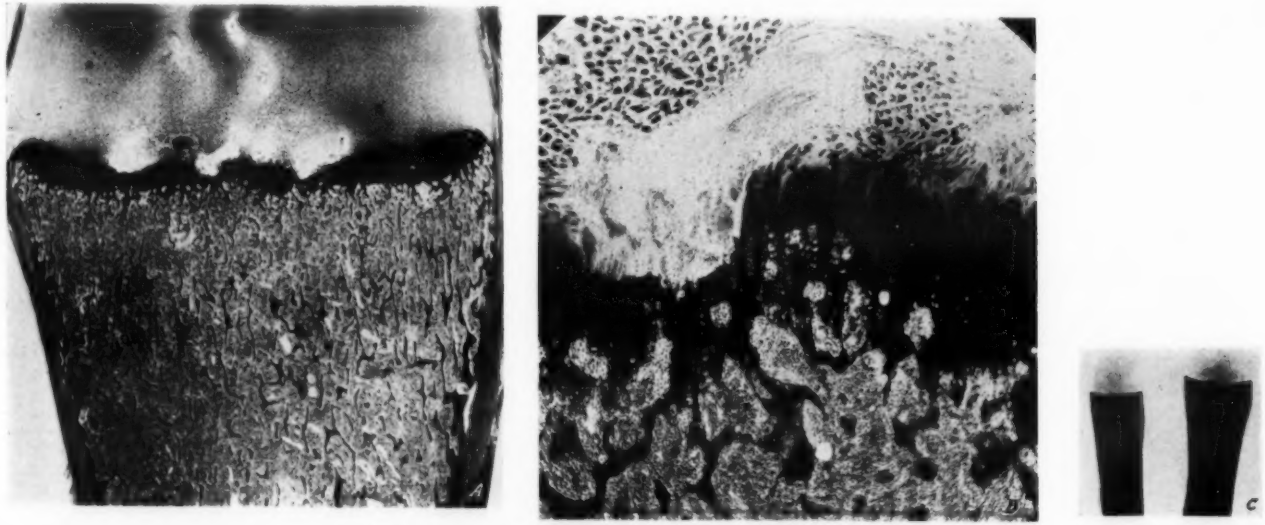

FIG. 3. J. M., CASE 4. TWO-YEAR-OLD COLORED CHILD

Rickets apparently absent in x-ray films (*C*), but the histologic examination of the bone showed evdence of a pre-existing rickets which had been almost completely healed by viosterol. Note the gaps in the cartilaginous zone and vestiges of uncalcified osteoid beneath the cartilage.

normal architecture. Case 3 is that of a fourteen months old colored child who had been given irregular amounts of cod liver oil after the age of six months. When seen at the age of twelve months, she presented marked rickets in her extremities and ribs. She was given 40 drops of viosterol daily for two months prior to her death. The x-ray films and the histologic sections of the bones showed that at the time of death the rickets was in the process of healing and that un-

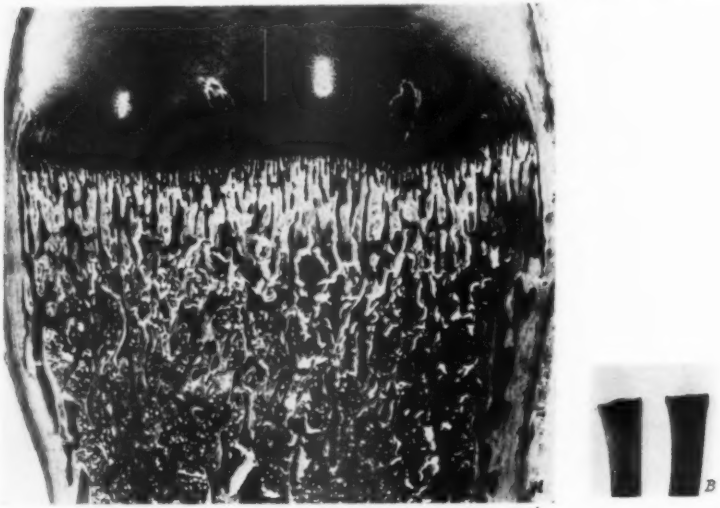

FIG. 4. J. C., CASE 7. TO ILLUSTRATE THE NORMAL APPEARANCE OF THE BONES IN A TEN-MONTH-OLD WHITE CHILD RECEIVING 20 DROPS OF VIOSTEROL DAILY, FOR FIVE MONTHS, AS A PROPHYLACTIC MEASURE

calcified tissue was still present in the metaphysis. The healing did not differ from that induced by cod liver oil or by ultra-violet light. Case 4 probably also belongs in Group I. In this instance, although the x-rays of the extremities and ribs were *apparently* normal (fig. 3, *C*), the histology of the bones (fig. 3, *A* and *B*) revealed evidence of a pre-existing rickets which had been healed nearly completely by viosterol. The vestiges of rickets were evident from the presence of uncalcified osteoid immediately under the cartilage, and of gaps in the

cartilaginous zone, indicating the points where the cartilage was invaded by blood vessels. However, the provisional zone was well calcified and the trabeculae of the shaft were devoid of osteoid.

Group II includes nine children given viosterol as a prophylactic against rickets. The duration of viosterol feeding varied from twenty-three days to thirteen and a half months. In none of these cases was rickets present, even in Case 5, that of a colored infant receiving but 5 drops, or only about 415 Steenbock rat units, of viosterol daily for thirteen and a half months. Signs of vitamin D over-dosage were likewise not found in the bones or in the soft tissues, including the kidneys—this in spite of the fact that the majority of these children were afflicted with chronic debilitating ailments during life. The x-ray and histologic appearance of a bone of a typical case in this group is shown in figure 4. The bone of this ten months old white child, who had received 20 drops of viosterol daily for five months, appears well calcified and of normal structure.

In contrast to the supposition that excess amounts of vitamin D produced hypermineralization of the ends of the bones in children, György (39) described just the opposite effect, namely, subepiphyseal osteoporosis. György's patient was a six months old infant suffering from otitis media and a secondary anemia. He was given a diet rich in vitamins, including 10 drops of Vigantol daily, and exposures to the sun's ray for a period of fifteen minutes daily. After three weeks on this therapy the child developed edema and cyanosis. The urine contained albumin and the stools were loose. On admission to the clinic the edema of the lower extremities was still present but the urine contained only traces of albumin, a moderate number of granular casts and fat droplets. The heart was enlarged to the left and the blood pressure was 95/75 mm. Hg. The concentration of hemoglobin in the blood was 50 per cent. The non-protein nitrogen of the blood was 24, the cholesterol 62, the serum calcium 8.6 and the serum inorganic phosphorus 3.3 milligrams per cent. The child recovered completely, except that the x-ray films of the long bones showed areas of rarefaction beneath the terminal zones.

György concluded that the child suffered from hypervitaminosis D, although he did not entirely dismiss the possibility of a congenital anomaly of the kidney or of a lipoid nephrosis in spite of the absence

of azotemia or of hypercholesteremia. The moderate *hypocalcemia* and *hypophosphatemia* he explained on the basis of renal damage, but such an explanation is not in accord with all experimental and clinical observations on renal insufficiency or on over-dosage with vitamin D. Excess amounts of vitamin D nearly always produce a *hypercalcemia*, *hyperphosphatemia*, or both; and if the kidneys are damaged, the predisposition to *hyperphosphatemia* is even greater and the azotemia is more pronounced. In György's patient the blood non-protein nitrogen was but 24 milligrams per cent, indicating no renal impairment; and the calcium and phosphorus concentrations of the serum were lower than the normal values for a child of this age. The only other evidence which György brought forward as indicative of vitamin D intoxication, was the presence in the x-ray films of the long bones of areas of lesser density immediately adjacent to the terminal zones. György compared these areas with the subepiphyseal osteoporosis in rats which results from feeding diets low in calcium and extremely large doses of irradiated ergosterol (40, 41). However, in spite of the superficial resemblance, examination of the x-ray films of his case reveals that such rarefaction resembles more closely that seen in the bones of rachitic children with pronounced osteoporosis, in whom vitamin D brings about a more rapid effect in the rachitic metaphysis and in the terminal zone of the bone than in the shaft, or that of children suffering from chronic ailments, such as tuberculosis, celiac disease, nutritional edema, or anemia. Such osteoporotic areas also simulate those of recently healed syphilis or scurvy. X-ray films of cases of osteoporotic rickets, treated with viosterol and showing such an area of decreased density, are shown in figure 5. In neither of these cases was there evidence of hypervitaminosis clinically or chemically. However, the clinical description of György's case and some of the chemical findings suggest that the edema might be due to a chronic hypoproteinemia rather than to renal impairment, and that the osteoporosis was merely the imprint left on the osseous system by the chronic metabolic disturbances. We have recently observed a case of nutritional edema in a colored child two and a quarter years of age, who had not received vitamin D prior to admission to the hospital, in whom the physical and chemical findings were similar to those described by György in his patient. In fact, before coming to our clinic,

she was seen in another hospital and treated as a nephritic because a few red cells were seen in the urine. On admission to the Harriet Lane Home, it was found that her non-protein nitrogen in the blood was but 17.8 milligrams per cent; total protein ranged between 2.6 and 3.3 (A/G = 0.98 and 1.4); cholesterol varied between 40 and 68; serum calcium 9.5 and serum inorganic phosphorus 4.5 milligrams per cent. The hemoglobin ranged between 62 and 80 per cent. The

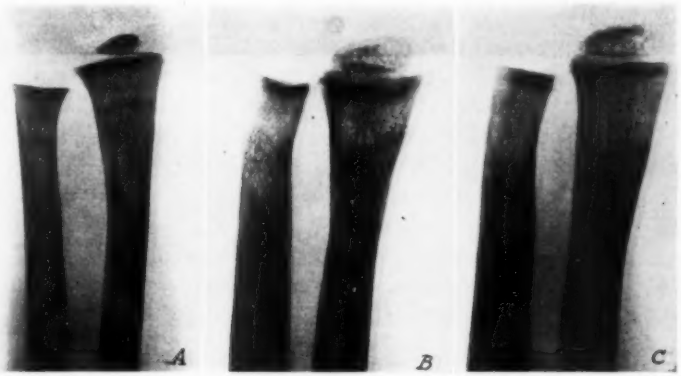

FIG. 5. ILLUSTRATES OSTEOPOROSIS OF THE RADIUS AND ULNA IN TWO CASES OF TREATED RICKETS

(*A*) A colored girl who had had active rickets at the age of eight months and had received 10 drops of viosterol daily for three months at the time the x-ray was taken. (*B*) A colored female of twenty-seven months whose rickets was healing spontaneously. She was placed on 20 drops of viosterol daily. (*C*) X-ray film of the same patient, taken three months later, showed that the rickets had healed completely and that the osteoporosis was still noticeable beneath the terminal ends of the shafts.

urine contained small amounts of albumin but no casts. The phenolsulphonphthalein excretion was 55 per cent in two hours, and the blood pressure was 110/80 mm. Hg. The stools were loose and frothy and resembled those seen in celiac disease. The x-rays of the long bones showed marked osteoporosis and possibly scurvy—the latter possibly being responsible for the hematuria. Because of the hypoproteinemia and hypocholesteremia, the patient was given a diet high in pro-

tein and cholesterol with the result that her symptoms disappeared quite promptly and the chemical constituents of the blood returned to their normal values.

It is possible, therefore, that György's patient was suffering, not from a vitamin D intoxication, but from a combination of nutritional disturbances such as mild scurvy with hematuria, anemia, and nutritional hypoproteinemic edema. When the patient was hospitalized and the dietary faults were corrected, the general condition improved, but the rarefaction of the bones, which took place during the period of malnutrition, remained for some time.

SUMMARY

1. Necropsies of thirteen children receiving standardized viosterol, in doses ranging from 5 to 50 drops for periods of twenty-three days to thirteen and a half months, failed to show evidence of toxicity in the soft tissues or in the skeletons.

2. Histologic examination of the bones of some of the subjects, who had received doses of viosterol, revealed that the dense ends seen in the x-ray films are indicative of *superior* rather than of *abnormal* calcification.

3. One of the children had had disseminated tuberculosis from early childhood; in him calcification was found in no other soft tissue in the body except the peribronchial lymph nodes and in tubercles.

4. One of the colored children of the group received but 5 drops, or 415 Steenbock units, of viosterol daily, as a prophylactic measure, from the first month of life until his death at the age of fourteen and a half months. His bones showed that this amount of viosterol was sufficient to completely protect him against rickets.

We are indebted to Dr. E. A. Park for his invaluable help in interpreting the histologic sections of the bones.

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THE MECHANISM OF ANAEMIA IN INFANCY

PHYSIOLOGICAL ANAEMIA[1]

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The concept of "physiological anaemia" of infancy has undergone considerable revision in recent years. Only a few years ago it was generally held that a relative anaemia was to be expected throughout the first year of life and that, since it was "physiological," it was unnecessary to try to do anything about it, unless it became more severe and entered the realm of the "pathological." Where the dividing line lay between the physiological and pathological was left to the judgment of the individual physician. Since the work of Helen MacKay in London, it has come to be recognized that this "physiological" anaemia of infancy is actually due to various extrinsic factors that, to a large extent, can be removed. The term "physiological" therefore is being increasingly used to cover only that short period of adjustment to extra-uterine life during which the haemoglobin is falling from the high level at birth to the lower levels of the first year of life. The work reported in this paper is a study of the factors responsible for this period of adjustment.[2]

The duration of the period of adjustment can best be judged from a comparison of two series of haemoglobin determinations in Charts 1 and 2. In Chart 1 are contained the observations on cases in the Florence Crittenden Home, an excellently run institution, where the babies, while being cared for by their mothers, are kept in a ward with little effort at complete segregation. The shaded line represents the average

[1] Aided by the Howland Memorial Fund.

[2] In this paper I have not attempted to review literature. Many of the observations recorded here have been made previously by others. The papers to which reference is made are parts of a study of the mechanism of various forms of anaemia occurring in infancy, of which this paper is also a part.

of these observations and the lines denoting the limits of variation are drawn by free hand to include between them all but very aberrant haemoglobin values. In Chart 2 are contained the haemoglobin curves in a second series of normal cases drawn from the metabolism ward of the Harriet Lane Home where the infants were segregated from the other patients and were almost entirely free from infection or even exposure to infection. The curves are plotted against the average and limits of variation taken from Chart 1.

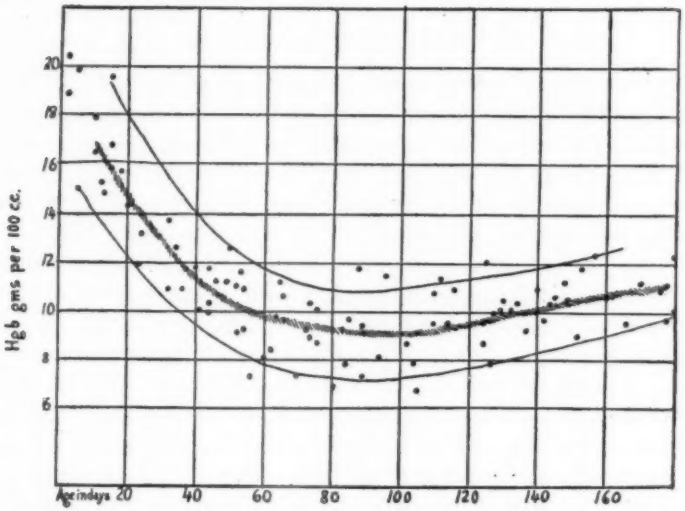

CHART 1. HAEMOGLOBIN VALUES OBTAINED FROM BABIES IN THE FLORENCE CRITTENDEN HOME

Note: For explanation see text

It is readily seen that for about six or eight weeks there is no difference between the two series, but that, from this point on, the haemoglobin values of the hospital cases tend to lie along the upper limit of variation of the Florence Crittenden Home cases. This evidently means that the extrinsic factors that influence the haemoglobin level do not begin to play a dominant rôle until the second month of life, and that up to this time the factors that determine the normal fall

in haemoglobin are intrinsic and common to all infants.[3] We may therefore confine the period of physiological adjustment in the normal baby to the first two months of life, although undoubtedly it may vary in individual cases.

Increased blood destruction has been generally assumed to be the factor responsible for the fall in haemoglobin. This assumption has been made on two grounds: (1) the presence of an increased bilirubin

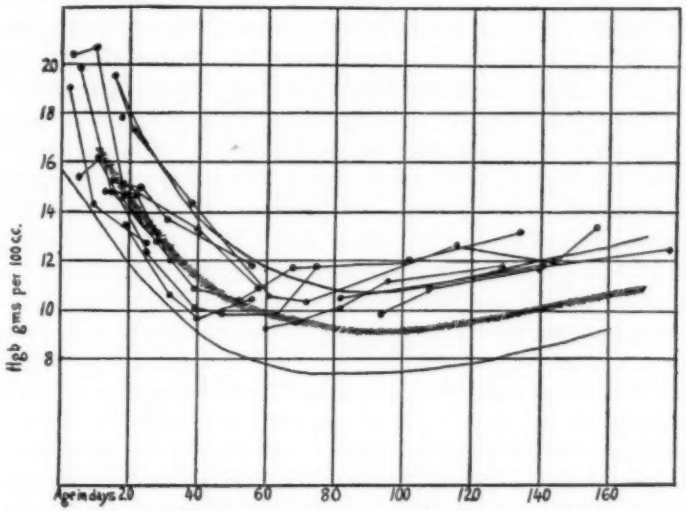

CHART 2. HAEMOGLOBIN VALUES OBTAINED FROM BABIES ON METABOLISM WARD OF HARRIET LANE HOME

Note: For explanation see text

content of the serum, lasting for several weeks; and (2), a belief that the rapidity of the fall in haemoglobin could only occur as a result of rapid destruction. While both these reasons appear to be valid grounds for the belief in the importance of blood destruction, it seemed worth while to attempt, if possible, to gain some idea of its magnitude.

[3] The babies in both series came from the same social stratum and it is unlikely that the difference between the two series could be explained by antenatal conditions.

This has been done through measurements of the daily excretion of urobilin in the stools.

UROBILIN EXCRETION AS A MEASURE OF BLOOD DESTRUCTION

In a recent paper (1), the relation between blood destruction and urobilin excretion was discussed. A review of the literature yielded no proof of any constant relation between the total excretion of urobilin and the amount of pigment made available for excretion either by destruction of blood or by the injection of laked blood. On the other hand, it was shown that the ratio between the total urobilin excretion and the calculated total haemoglobin of the body was approximately constant within the same age group, despite wide variations of haemoglobin percentage and body weight. In other words, the urobilin excretion in the stools depends largely on the total amount of circulating haemoglobin in the body, from which it is derived as an end-product of blood destruction. It is natural, therefore, to consider the urobilin-haemoglobin ratio, expressed as milligrams of urobilin excreted per gram of circulating haemoglobin, as an index of blood destruction.

In a previous paper (2), in which the mechanism of a number of cases of infantile anaemia were analyzed, I attempted to test the urobilin-haemoglobin ratio as an index of blood destruction by balancing it against the reticulocyte percentage (reticulocyte-red-cell ratio) used as an index of blood formation. To facilitate balancing, the use of "units" was introduced, a "unit" of blood destruction being the urobilin-haemoglobin ratio that has been found to be the average in a large number of normal infants; the "unit" of blood formation, the average reticulocyte percentage in normal infants. If the urobilin excretion can be used as a measure of blood destruction as the reticulocyte percentage is used to measure blood formation, then a preponderance of units of one or the other process should be followed by a rise or fall in haemoglobin and red cells, according to the process which predominates. In the cases studied this was found to be true.

METHOD OF PRESENTATION

In the work reported here the same method has been used, except that "units" have been dispensed with, their place being taken by a rough balancing in the charts. The urobilin-haemoglobin ratio has

been calculated as in the previous paper (1). Total haemoglobin is calculated on the assumption that blood volume constitutes 7.6 per cent of the body weight, by the formula:

$$\text{Total Hgb} = \frac{\text{Hgb (gms. per 100 cc.)} \times 76 \times \text{wt. (kgs.)}}{100}$$

Justification for the use of this formula has been given in the same paper. The daily urobilin excretion in the stools in milligrams is divided by the total haemoglobin in grams to obtain the ratio which

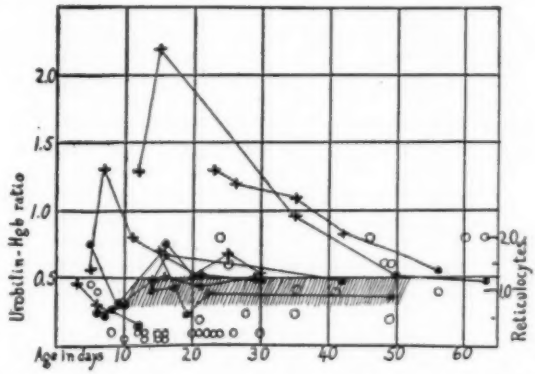

CHART 3. UROBILIN-HAEMOGLOBIN RATIO AND RETICULOCYTE PERCENTAGE IN NORMAL BABIES

Note: The solid circles represent values for urobilin-haemoglobin ratio obtained when the haemoglobin was stationary. The crosses represent values for urobilin-haemoglobin ratio obtained when the haemoglobin was falling. The hollow circles represent reticulocyte percentage.

expresses the excretion of urobilin per gram of circulating haemoglobin. This has been found in the normal infant to vary between 0.3 and 0.5 with an average of 0.4. This "normal" ratio is expressed in the charts by a shaded area. The reticulocytes are so charted that 1 per cent falls on the same line as a urobilin-haemoglobin ratio of 0.4. In this way in the charts a rough balance is attained.

OBSERVATIONS

In Chart 3 are contained the urobilin-haemoglobin ratios and the reticulocytes, plotted against the age in days. The solid circles repre-

TABLE I*

Normal babies

NO.	NAME	DATE	AGE	WGT.	HGB.		URO-BILIN EXCRETION IN STOOL	URO-BILIN TOTAL HGB. RATIO	RETICULOCYTES
					Per 100 cc.	Total			
			days	*kgs.*	*gms.*	*gms.*	*mgs.*		
1	Cassel B. 11/28/32	11/30–12/4/32	4	3.5	12.9	34	13	0.37	1.0
		12/4–8	8	3.5	10.7	28	8.5	0.30	occas.
		12/8–12	12	3.5	11.5	31	5.5	0.18	occas.
2	Englar B. 1/18/33	1/21–25/33	5	3.4	15.1	40	30	0.75	0.5
		1/25–29	9	3.5	14.8	40	12	0.31	occas.
		1/30–2/3	14	3.5	14.5	39	23	0.57	occas.
		2/3–7	18	3.5	14.5	39	26	0.64	
3	Tamberino B. 4/1/32	4/5–9/32	6	3.5	15.3	41	11	0.27	4†
		9–11	9	3.5	16.5	44	14	0.32	occas.
4	Tamberino B. 4/16/31	4/20–22/31	5	3.5	23.8	63	35	0.56	occas.
		4/22–24	7	3.6	22.0	60	80	1.30	occas.
		4/24–29	11	3.7	19.5	54	43	0.80	occas.
		5/5–9	21	4.0	14.8	45	23	0.51	0.5
		5/18–21	33	4.4	12.9	43	21	0.49	0.5
5	Stevens B. 3/20/31	3/26–27/31	6	3.5	21.0	56	11	0.20	1.0
		3/31–4/2	12	3.4	21.0	54	12	0.22	occas.
		4/2–4	14	3.5	17.8	47	22	0.47	occas.
		4/4–6	16	3.6	15.9	44	30	0.68	occas.
		4/12–14	24	3.8	12.6	36	17	0.48	2.0
		4/30–5/2	42	4.3	13.3	43	20	0.47	1.0
		5/6–5/8	49	4.5	12.9	44	21	0.48	0.5
		5/19	60		10.6				0.5
6	Nance B. 3/11/31	3/23–25/31	13	3.7	15.3	43	31	0.70	occas.
		3/31–4/2	19	4.0	15.3	47	11	0.23	occas.
		4/2–6	22	4.2	14.2	46	18	0.39	occas.
		4/22	42		11.9				
		4/28–30	49	5.0	11.9	45	16	0.36	1.5

* In order to save space in the table the figures for urobilin excretion have been averaged usually in four-day periods, while the observations were made in two-day periods. The points in Chart 3 have been plotted from this table. The points in Charts 4 to 7, on the other hand, have been taken from the original observations, and, therefore, will at times show variations from the figures recorded in the table.

† Fourth day.

TABLE I*—*Concluded*

NO.	NAME	DATE	AGE	WGT.	HGB.		UROBILIN EXCRETION IN STOOL	UROBILIN TOTAL HGB. RATIO	RETICULOCYTES
					Per 100 cc.	Total			
			days	*kgs.*	*gms.*	*gms.*	*mgs.*		
7	Kent B. 4/6/31	4/20–22	15	3.05	18.9	44	15	0.34	1.5
		4/22–24	17	3.1	(18.0)	42	25	0.60	
		4/24–27	20	3.2	17.2	42	15	0.36	1.5
		4/27–29	22	3.2	14.3	35	18	0.51	1.5
		5/5–9	31	3.4	12.6	33	17	0.52	1.5
8	Whittington B. 2/23/31	3/8/31	13	2.9	14.8	33			occas.
		3/9–11	15	2.9		(34)	14	0.41	
		3/12	17	2.9	15.7	35			
		3/11–17	19	3.0	14.7	35	15	0.43	occas.
		3/19–21	25	3.2	14.3	35	26	0.75	occas.
		3/21–25	28	3.3	13.1	33	17	0.52	0.5
		3/27–29	33	3.4	12.0	31	8	0.26	0.5
9	Keenan B. 12/25/30	1/2/31	8	3.8	17.6				
		1/6–7	12	3.8	(16.0)	47	60	1.30	occas.
		1/7–12	15	4.0	14.2	42	94	2.25	occas.
		1/27–31	35	4.7	10.9	39	38	0.97	1.0
		2/11–14	49	5.3	10.5	42	22	0.52	1.5
		2/26–28	63	5.7	12.0	51	25	0.49	2.0
		3/15–17	80	6.0	12.7	58	19	0.32	0.7
10	Buyman B. 12/15/30	1/2/31	18		15.0				
		1/2–6	20	3.7		42	60	1.40	occas.
		1/7–11	25	3.8	13.2	38	42	1.1	1.5
		1/17–21	35	4.1	10.6	33	37	1.1	1.5
		1/23–29	42	4.3	9.6	31	22	0.71	2.0
		2/8–10	56	4.8	10.5	38	21	0.55	1.0

sent the ratios when the haemoglobin was stationary or rising temporarily; the crosses, the ratios when the haemoglobin was falling; the hollow circles, the reticulocyte percentage. Several points are clear. (1) Of the ten cases studies (see also table 1), seven had a urobilin-haemoglobin ratio that at some time within the first thirty days was above 0.5. The remaining three were insufficiently studied. In 3 of the 7 cases the urobilin excretion was high enough to be considered excessive. (2) In general the periods in which the urobilin excretion was high were periods of falling haemoglobin, and those in which it

was low were periods of stationary or temporarily rising haemoglobin. There was, however, no strict parallelism between the height of the urobilin excretion and the rate at which the haemoglobin fell. (3) The reticulocytes, averaging about 1 per cent in the first week, fell to the point of almost complete disappearance during the next two weeks, then slowly rose, reaching as high as 3 to 4 per cent by the end of the second month. It is striking that at this time the haemoglobin was stationary or rising in all the cases, although the urobilin excretion was as high as it was earlier when the haemoglobin in most of the cases was falling. In two cases, the reticulocyte count was high at an earlier period than usual. In one of these (B) the urobilin-haemoglobin ratio was also high (1.3), in the other the haemoglobin was temporarily stationary.

Individual charts have been prepared to show in more detail the relation of the changes in haemoglobin to the balance between reticulocyte percentage and the urobilin-haemoglobin ratio. In these charts the reticulocytes are designated by the crosses. The shaded curve in the portion of the chart in which the haemoglobin is plotted represents the average haemoglobin curve taken from Chart 1. To economize space those charts that have been extended only up to the thirtieth day and include, therefore, only the period of falling haemoglobin, have been omitted. They show merely what is clear from Chart 3, namely the relation between falling haemoglobin and high urobilin excretion. In Charts 4 to 7 the observations have been extended to include the period of rising haemoglobin beyond the fortieth day. At about the point at which the haemoglobin curve starts to rise, it may be observed that the rising reticulocyte curve tends to cross the line representing the falling urobilin-haemoglobin ratio. St. (chart 7) is an exception, in that the reticulocyte curve crossed the curve of urobilin excretion at about the end of the third week and remained elevated for a short time, accompanied by only a temporary break in the downward course of the haemoglobin curve.

It is evident from these studies that increased blood destruction is not alone responsible for the rapid fall in haemoglobin during the first three weeks of life. We must take into account that during this period the rate of blood formation as indicated by the reticulocyte percentage is at a low point, so that even a moderate blood destruction results in a

falling haemoglobin. It is not until the fortieth day or later that the rate of blood formation rises sufficiently to balance the rate of destruction.

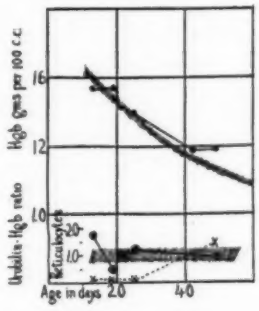

CHART 4. CASE 6

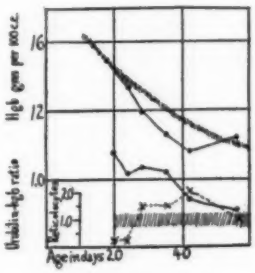

CHART 5. CASE 10

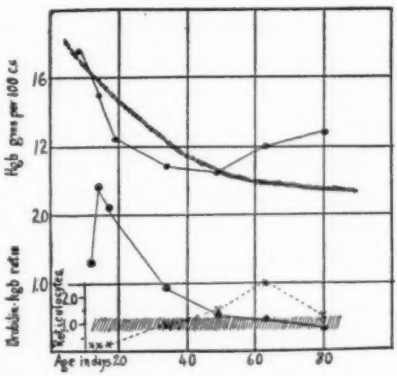

CHART 6. CASE 9

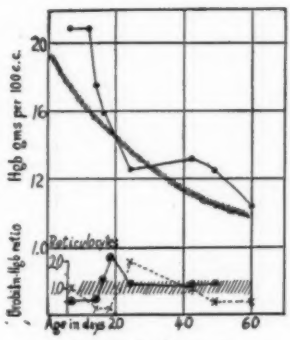

CHART 7. CASE 5

Note: In this and all subsequent charts, the continuous line and solid circles in the upper portion of the chart represent haemoglobin. The continuous line and solid circles in the lower portion represent urobilin-haemoglobin ratio. The crosses and broken line represent reticulocyte percentage.

PREMATURE BABIES

In premature babies the course of events is somewhat different. The reticulocytes rise as in full-term babies, reaching even higher

values, but there is no accompanying rise in haemoglobin, unless iron is supplied. This was pointed out and discussed in a previous paper

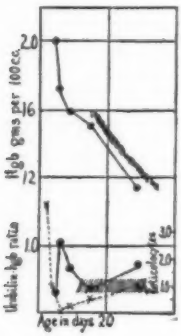

CHART 8. PREMATURE INFANT

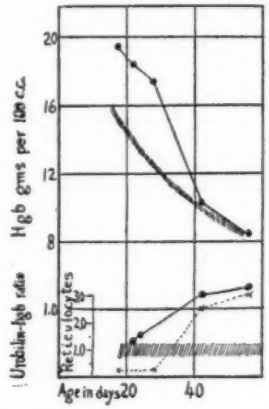

CHART 9. PREMATURE INFANT

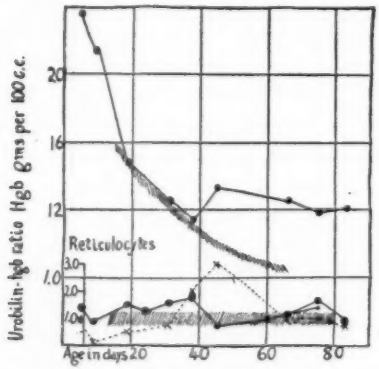

CHART 10. PREMATURE INFANT

(3). The explanation that seemed most likely was that the blood-forming tissue was unable to form completely mature cells rapidly enough to supply the normal demand for blood formation, so that an increased number of young forms were thrown out into the blood. The absence of nucleated red cells would merely indicate that the

inability of the bone marrow to put out mature forms was not a very serious matter.

There is, however, another possibility: namely, that the relative rate of blood destruction is greater than that occurring in full-term infants, so that there would have to be a greater compensatory rise in blood formation, with a greater output of reticulocytes. This possibility has been studied and the results are contained in charts 8, 9 and 10. In the first two (H and Bu), the course of the urobilin differs from that of full-term infants in a tendency to rise after the thirtieth day so that the reticulocyte and urobilin curves, instead of crossing, remain parallel with the curve of urobilin excretion slightly above that of the reticulocytes. It thus appears that this second hypothesis holds for at least some of the cases, but the number of observations is too limited thus far to permit a generalization. The third case (N) forms an interesting exception. Up to about the fortieth day of life the curves were similar to that of the other two cases, and the haemoglobin followed the average curve for premature babies, as determined in the previous article. Then the course of events changed and the curves from that time on are typical of those of a normal full-term infant. The only cause that could be ascertained for this abrupt change was a single dose of medicinal iron given by mistake on the fortieth day of life. Whether or not this dose of iron was the determining factor in the change of events can be decided only by further study.

SUMMARY

Studies of urobilin excretion and reticulocyte percentage have been made to determine the mechanism of the "physiological" fall in haemoglobin and subsequent adjustment to the normal level of infancy. It was found that, although there was evidence of increased blood destruction which might at times be excessive, the increased destruction did not wholly account for the rapid fall in haemoglobin. Combined with it was a great reduction in reticulocytes lasting for about three weeks. The reticulocytes then began to increase in numbers while the urobilin excretion returned to normal figures so that a tendency for the two curves to cross becomes apparent. This crossing, occurring usually between the fortieth and fiftieth day, indicates the develop-

ment of a predominance of the factor of blood formation and as should be expected is accompanied usually by a rise in haemoglobin. Thus, while the early fall in haemoglobin is conditioned largely by increased destruction of blood, the later adjustment is determined by an increased formation.

In the case of the premature, to judge from a smaller number of cases, the rate of blood destruction tends to remain above the normal level. A predominance of blood formation does not take place, with the result that the haemoglobin remains low. One case that proved an exception, suggests a mechanism by which iron exerts its effect on the course of the haemoglobin that deserves further confirmation and study.

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LEAD POISONING: REPORT OF A CASE IN A CHILD WITH EXTENSIVE PERIPHERAL NEURITIS

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INTRODUCTION

Symptoms of encephalitis usually dominate the clinical picture shown by children suffering from lead poisoning. The disorders of the gastrointestinal tract and of the blood are not uncommon, but peripheral neuritis is distinctly more rare than it is in adult plumbism. We have recently had a child on our wards with lead poisoning as a result of which the peripheral nerves were involved, showing not only generalized paralysis but also extensive sensory changes, a somewhat uncommon development.

History. M. E. Y., H.L.H. 67063, Path. No. 12168, a three and a half year old colored girl, was brought to the Harriet Lane Home August 25, 1931, because of weakness of her extremities and difficulty in swallowing. Her family consisted of her parents, both quite healthy in their late thirties, a brother of nine and two sisters of four and two, all in good health. No history of familial disease was obtained.

The patient was the result of a normal pregnancy and labor, weighing seven and a half pounds at birth. Her infancy was uneventful and her development average. Except for a lack of Vitamin D during her first year, the feeding was satisfactory. She had never been ill until she was two years old, when with the story of vomiting, abdominal pain and fever, she was admitted to the ward. Pus was found in her urine and pyelitis considered the cause of her symptoms. In two months she was symptom-free and her urine remained clear. No other untoward event had occurred until the present illness.

Three weeks before coming to the hospital the patient had an attack of persistent vomiting, lasting three days but unaccompanied by other symptoms. The fourth day she retained her food and the vomiting did not recur. During the next few days there was increasing weakness beginning in her legs and moving progressively upward, so that by the end of the first week of illness the child had lost all desire to play, was unable to stand alone and would slump down when she was

propped up in the bed. At this same time she objected to being picked up, saying that her legs were sore. The family doctor discovered a slightly swollen, painful right knee, and thought the condition to be acute rheumatic fever.

The weakness progressed and the child became bedridden. Speech was difficult, and cries of pain were the only audible sounds she made. Four days before we saw her, her arms and hands became very weak and the following morning she developed marked dyspnea. The day before admission she had difficulty in swallowing food and choked several times when attempting to drink water. All through her illness her mind remained clear, and she could understand what was said to her and indicated the correct reply. There was no other symptom noted up to the time of admission.

She presented a very pitiful picture when she was brought into the ward. Her thin arms and legs, having lost all power of motion, hung flail-like from her body. Her face, particularly the left side, would occasionally twitch convulsively. She centered her whole attention on breathing, giving little heed to her surroundings, and answering questions in hurried whispered monosyllables. Her skin felt normally warm and quite dry; no areas of discoloration or eruption were seen. The lymph glands were slightly enlarged. The eyes, ears and nose were normal, the lips dry and the tongue coated. The teeth, gums and buccal surfaces were normal, except that all the mucous membranes showed a slight pallor. Her tonsils were enlarged. No abnormalities were found in the lungs or abdomen and, except for a rapid rate, (160) the heart was normal. The leg bones showed slight bowing due to old rickets.

Our interest was centered chiefly in the neurological examination. A complete flaccid paralysis involved both legs, both arms, the trunk muscles up to the chest and the diaphragm. The accelerated, irregular breathing was carried on entirely by the intercostals and accessory muscles of respiration. The facial muscles were strong but occasionally gave very fine, almost fibrillary twitchings, on the left side. The deep reflexes of the arms and legs and the abdominal reflexes were absent. No abnormality of the cranial nerves was made out except for a slight weakness of the pharyngeal muscles, resulting in some difficulty in swallowing. Examination of the eye-grounds was negative. There was complete anesthesia to touch and pain over the whole trunk and all four extremities. Even very deep pin-pricks were not felt. However, when the thigh muscles were pinched very hard, some evidence of pain was elicited. No areas of hyperesthesia were found. The face apparently was unaffected and the scalp was sensitive to pain as far back as the occiput. More detailed sensory tests were not possible because of the patient's weakness and lack of coöperation. Several days after admission she was unable to feel tuning-fork vibrations over the bones of the arms and legs.

Shortly after her coming into the ward a fluoroscopic examination was done to determine the degree of diaphragmatic palsy. This was found to be complete. It was noted, however, during the procedure that the lower ends of the radii and ulnae were much denser than normal. Our attention was then directed to the possibility of lead poisoning as the cause of the extensive peripheral neuritis.

X-ray photographs of the long bones confirmed our previous observation. With this definite suspicion in mind we questioned the parents further, and discovered that, a month before the onset of the first symptoms of illness, the patient had amused herself playing among the paint pots of a neighbor who had recently painted his roof. More than once the child had come home with red paint on her hands and face. There was no other history of contact with lead or ingestion of other poisonous substance.

Examination of the blood gave the following results: Hemoglobin 60 per cent; Red blood cells 4,410,000; White blood cells 19,500 with 75 per cent polymorpho-

FIG. 1. A LONGITUDINAL SECTION FROM THE SCIATIC NERVE STAINED WITH SCHARLACH R AND MAGNIFIED 825 TIMES

Extensive myelin degeneration is indicated by the dark bands

nuclears; 20 per cent lymphocytes; 4 per cent monocytes. The stained film showed a secondary anemia with marked anisocytosis and poikilocytosis. There was punctate basophilic stippling of the red blood cells. A few hyaline casts and a trace of albumin were found in the urine, which was otherwise negative. The intracutaneous tuberculin test and the blood Wassermann were negative. The Schick test was positive.

Lumbar puncture gave clear fluid under normal pressure. There was no globulin present and no pleocytosis. Colloidal mastic test 0000000000 and the Wassermann negative.

The difficulty in swallowing made gavage necessary during the greater part of

her stay in the hospital. She was put on a milk diet and given 40 drops of Viosterol daily in an effort to cause deposition of lead in the bones, but no significant change occurred in her condition. At times there would seem to be an increase in strength and she would be more alert, but the general tendency was downhill. Atrophy of the muscles became more marked and the paralysis and anesthesia remained about as they were on admission. Control of the sphincters was maintained throughout her illness. Herpes developed on her lower lip during the

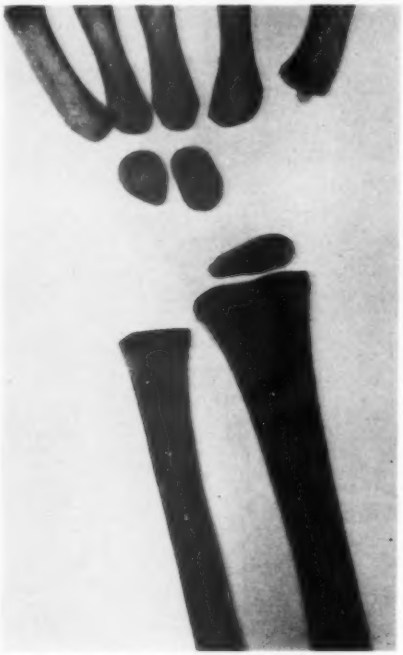

FIG. 2. X-RAY OF RIGHT WRIST SHOWING THE ZONES OF GREATLY INCREASED DENSITY AT THE POINTS OF GROWTH IN THE RADIUS AND ULNA

second week of hospitalization. Seventeen days after coming to the hospital her temperature suddenly rose from the normal level it had maintained to 40°C. She became comatose and her few remaining muscles were in a convulsive state. Efforts to relieve her did not avail, and she died within three hours after the convulsion began, six weeks after the onset of her illness.

Pathological findings. No gross pathological lesions were found in any of the organs at autopsy and no adequate explanation was advanced for the sudden ter-

minal convulsions and hyperpyrexia. On microscopic examination the kidneys showed a few small areas of tubular degeneration with calcification and round-cell infiltration. Occasional casts were seen in the tubules. The glomeruli were intact and no change was seen in the kidney pelvis. The other organs were normal.

The brain showed no change, nor did the medulla, spinal cord, anterior roots, posterior roots or spinal ganglia. However, in sections taken from various striated muscles, a remarkable degeneration of the peripheral nerves was quite obvious both in the sections stained with the Weigert myelin sheath stain and those stained with Scharlach R. for fat. This myelin degeneration was more marked in the nerves of the leg. This might be expected, since the lower extremities were the first to be involved. However, it was quite extensive in the arm also, being least

FIG. 3. (*a*) SPECTROGRAPH OF BONE FROM M. E. Y., SHOWING THE LINES CHARACTERISTIC OF LEAD; (*b*) SPECTROGRAPH OF LIVER SHOWING SIMILAR LINES

The arrows point to the lines characteristic of lead spectrum. The upper bar of the triplet represents the control spectrum of the upper electrode; the lower bar that of a known solution of lead sulphate and the middle bar the spectrum of the substance being tested.

of all in the phrenic nerve seen in sections from the diaphragm. No change, except possibly a slight atrophy, was found in the muscles themselves. As mentioned above, no lesion was observed in the spinal cord or its roots, although the same stains were used which showed the degeneration in the peripheral nerves.

A microscopic section of a rib showed the dense line of trabeculae on the diaphyseal side of the cartilage shaft junction which are characteristic of the effect of lead on the growing bone.

A spectrographic analysis was made of a small piece of the same bone. The lines characteristic of the emanation spectrum of lead were found on the spectrogram. A specimen of liver similarly analyzed also contained lead.

COMMENT

The question immediately arises whether we are justified in considering this unusual clinical picture a manifestation of lead poisoning

alone. When we think of the history of contact with paint, the many clinical signs of plumbism, and the demonstration of the metal in the child's tissues, little doubt remains that the patient was a victim of lead intoxication. There was no exposure known to arsenic, alcohol or other poison which could cause such extensive changes in the peripheral nerves. Infection seems unlikely as an etiological agent, since there was no illness preceding the onset of symptoms.

The patient's youth unfortunately prevented our getting a clear idea of the subjective sensations preceding the onset of paralysis and anesthesia. We do know, however, that she had pain in her legs which was intensified on being handled. We can only speculate as to whether it was a real hyperesthesia. The arthritis mentioned by the family doctor was, in all probability, a true lead arthralgia. The loss of cutaneous sensation both to touch and pain quite typically preceded the loss of deep sensation in the muscles.

The heavy line at the ends of the long bones first called our attention to lead as a cause of this child's illness. This emphasizes the importance of the phenomena described by Park, Vogt and others (1), as a diagnostic aid when lead poisoning is suspected in a growing child. The narrowness of the band of increased density makes us feel that the exposure to lead could have existed only for a comparatively short time. This is entirely consistent with the history.

Spectrographic studies of the body fluids and tissues are becoming increasingly popular as a clinical method for the identification of lead (2). As a qualitative test it is, when carefully carried out, quite as reliable as chemical analysis. Certain observers have criticized the method as being too delicate to distinguish between a pathological quantity and an amount of lead too small to produce clinical symptoms. Similar analyses from other patients on the same ward gave negative results.

Much controversy has gone on between neuropathologists over the site of the initial lesion in lead paralysis. Many types of palsy have been described, some with atrophy and others without; some completely flaccid, others with more or less spasticity, most of them purely motor, but some accompanied by various sensory changes. Correspondingly, there have been a great number of pathological lesions said to be the original ones initiating the train of symptoms. Degen-

eration of the anterior horn cells, anterior roots, peripheral nerves and neuromuscular spindles are all described. The many findings and theories are adequately reviewed and summarized by Hyslop and Kraus (3), who conclude that the whole nerve cell is probably affected from the beginning, and that the condition is a lead neuronitis. Spiller (4), in reporting the pathological findings in the central nervous system in a case of lead poisoning, expresses the belief that "It seems impossible to determine whether its effects are first manifest in alteration of the peripheral motor fibers or of the motor cell bodies of the spinal cord, but inasmuch as both peripheral nerve fibers and motor cell bodies are sooner or later affected, this question is not a very important one. The condition is, therefore, essentially a peripheral neurone disease or neuronitis."

LITERATURE

Attention was called to peripheral neuritis in the lead poisoning of children by Gibson, Love, Turner and others (5), who reported the large numbers of cases which occurred in Australia. They mentioned wrist drop and foot drop, commenting on the greater frequency of the latter as probably due to the greater fatigue of the legs in childhood. Although the pediatric literature abounds with reports of lead poisoning (6), encephalitis dominates the picture and little mention is made of the manifestations of peripheral neuritis, particularly sensory changes. Aub, Fairhall, Minot and Reznikoff (7), in their extensive review, consider sensory changes only as prodromata of paralysis or encephalitis.

In a few instances mention is made of tingling or painful extremities before the onset of a wrist or foot drop. We, ourselves, have seen one case of lead poisoning in which there was hyperesthesia of the legs, and another in which painful sensations were complained of in both arms and legs. We have been unable to find in the literature any case of lead poisoning with such extensive and severe sensory changes as in the one reported.

In this child the duration of the multiple neuritis was shorter than in most of the cases in the literature and it is interesting that the most severe, if not the only, demonstrable pathological lesions, were in the peripheral nerves. Other methods of fixation and staining

might possibly show slight protoplasmic alterations in the cell bodies or end organs, but they could hardly be in proportion to the extensive myelin degeneration of the nerves themselves.

Early in the fifth century Paul of Aegina (8), in writing of lead intoxication, mentioned that "wherefore in many cases it passed into epilepsy, to some there came loss of motion with sensation unhurt, to many both, and of those who fell victims to the epilepsy very many died." Notwithstanding the fact that sensory changes were mentioned so early, and that there has been a tremendous volume of literature on lead poisoning, anesthesia in connection with palsy has remained one of the rarer manifestations of plumbism. Some of the earlier observers went so far as to cite lead as a poison particularly affecting the nerves of motion which left sensation untouched.

In his unsurpassed monograph on the clinical manifestations of lead poisoning, Tanquerel des Planches (9) devoted a chapter to "Lead anesthesy." Out of 1493 patients with the various manifestations of intoxication from lead he observed a loss of sensation only eleven times. Three times this sensory loss was accompanied by weakness of muscles in the same part of the body, and in no case did the zone of anesthesia extend over a large part of the body surface. He stated that "The paralysis produced by lead preparations may consist of the loss of motion only in the parts enjoying at once both motion and sensibility. In other cases on the contrary, the sensibility only of these same parts is affected." And again, "In all observations of anesthesia, the coincidence of phenomena of general and primitive infection, produced by lead, has been noted. Usually this anesthesia comes on suddenly without being announced by symptoms . . . it often appears a while after the paralysis of motion, or it may be preceded by arthralgy, its direct opposite."

Oliver's (10) extensive experience with industrial lead poisoning in Great Britain led him to think that "In wrist drop there can occasionally be detected patches of anesthesia and analgesia on the inner and posterior aspects of the forearm. On the leg similar patches may be found when the lower extremity is involved. In females the loss of sensation may be such as to suggest a hysterical or functional origin of the anesthesia." This 'glove and stocking' type of anesthesia or paresthesia has been described by other authors, and Thomas (11)

mentions it in a case of generalized paralysis from which the patient recovered.

SUMMARY

A case of multiple peripheral neuritis with extensive paralyses and almost total anesthesia is reported in a colored girl of three and a half years suffering from lead poisoning of approximately two months' duration. The autopsy findings are given. Attention is called to the fact that grave sensory changes may occur in the lead poisoning of children.

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BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this journal.)

Die Virusformen. By FRANZ LUCKSCH. 230 pp. Illust. (*Robert Lerche, I. G. Calve'sche Universitäts-Buchhandlung, Prag, 1934.*)

Die Virusformen is a brochure dealing with viruses and the diseases caused by them. The diseases are divided into three groups: (1) the maladies caused by bacteria-like organisms, *e.g.*, Oroya fever, pleuropneumonia, typhus fever; (2) the diseases induced by primitive forms of life, *e.g.*, vaccinia, rabies; and (3) the maladies incited by "virus-enzymes," *e.g.*, Rous' sarcoma of fowls, fowl leukemia, foot-and-mouth disease of cattle, mosaic diseases of plants, bacteriophagy.

The first and the best part of the treatise deals with the names of viruses in general, with the results of work having to do with their cultivation, staining and filtration, and with the resistance of viruses to chemical and physical agents. In the second section, most of the virus diseases are discussed in detail. One wonders, however, why Rinderpest and hog cholera were omitted and why much of the recent work on yellow fever was not considered.

A great deal of the work on viruses is reviewed in an uncritical manner with the result that uninitiated students will probably become confused. The names of many authors are spelled incorrectly, for instance, (p. 15), Zinser and Bang for Zinsser and Tang, Elfort for Elford, and (p. 147) Richter for Ritter. In addition to the misspelling of names there also frequently occur inaccuracies in the statement of facts. On p. 15 Elford is said to have determined the size of the virus of foot-and-mouth disease by diffusion. He actually used ultrafiltration. On p. 24 Lewis is said to have cultivated the virus of yellow fever. As a matter of fact he only showed that it survived for 10 or 12 days in a certain kind of medium. On p. 24 Andrewes is said to have shown that a virus will not grow in tissues in the presence of immune serum. He really showed that a virus will multiply under such conditions, provided it comes in contact with the cells before they are placed in the immune serum.

Many workers in the virus field will object to having pleuropneumonia, agalactia, Oroya fever, scarlet fever, and the rickettsia diseases placed in the virus group. Others will not agree that postvaccinal encephalitis is caused by the direct action of vaccine virus on the central nervous system. Still others will undoubtedly deny that substances such as "virus-enzymes" exist. Finally, there is no convincing evidence that filterable forms of ordinary bacteria are in any way related to the viruses. Nevertheless, Dr. Lucksch has a right to his own opinions and his treatise will excite interest in the viruses, so that workers in the field should be familiar with it.

T. M. R.

Bone Growth in Health and Disease. By H. A. HARRIS. 248 pp. (*Oxford Univ. Press, New York, 1933.*)

The author's aim was apparently to describe "the biological principles underlying the clinical, radiological, and histological diagnosis of perversions of growth and disease in the skeleton." This aim, however, has not been entirely attained. The author seems more concerned with expounding his own views on "lines of arrested growth" rather than with a general discourse on bones in health and disease. Even when specific diseases are mentioned, the views and opinions are based nearly entirely on the author's own findings in a limited number of cases, with but little regard to what others have found in larger groups. Many pages are allotted to "lines of arrested growth," which the author has already handled elsewhere, but very little space is given to such diseases as *osteogenesis imperfecta* and *osteitis fibrosa cystica*. The former is not even listed in the index, and the latter is disposed of in nine lines, in spite of the interest attaching to the disease since 1926.

The author's views on rickets and vitamin D, for which he was awarded a prize by a Philadelphia medical society, are still current in the pages of the present volume. Thus, in spite of the well-established fact that vitamin D promotes calcification in membranous as well as cartilaginous bone, he argues that "vitamin D should be known as the vitamin controlling calcification in cartilage and not as *the* anti-rachitic vitamin" (p. 94). His misunderstanding of experimental rickets is also evident from the statement that "Wegner [who produced osteosclerosis by feeding phosphorus] at one and the same time defined two problems of particular recent significance: the transverse band of the bone in the metaphysis, on the one hand, and the changes in the bone due to disturbance in the calcium-phosphorus ratio, on the other" (p. 3). The last statement is, of course, questionable, since the phosphorus used by Wegner was *elementary phosphorus* and the amount given was in the neighborhood of only 0.2 mg. per day; which small amount could not have influenced appreciably the calcium and phosphorus ratio of the diet.

There is no excuse for omitting reference to the work of Eliot, Souther and Park on "Transverse Lines in X-ray Plates of the Long Bones of Children" [1927].

Nevertheless, the book possesses commendable qualities. The illustrations are exquisite and clear. The discussions on "Growth of Cartilage" and "Bone Formation" are well presented, as is also the chapter on "Costal Cartilages."

The book may be useful to those already acquainted with the subject, but is by no means suitable as a text for the beginner, or as a reference book for the researcher.

D. H. S.

The Surgical Pathology of the Diseases of Bones. By ARTHUR E. HERTZLER. 1930–31. 301 pp. 211 illust. (*J. B. Lippincott & Co., Phila., 1930–31.*)

In this volume of 272 pages the author gives a clear exposition of all the chief diseases and tumors of bone.

The acute inflammatory diseases of bone are divided into those resulting from infection from without and those of the blood-borne type. A chapter is added on osteomyelitis in special regions. The clinical features and the gross and microscopic pathology are excellently handled. As in the rest of the book, treatment is not emphasized and the author confines himself strictly to the pathological features of the disease which he feels will be of benefit to the clinical surgeon. The chapters devoted to chronic inflammation of bone and to specific infection are perhaps too brief. Paget's disease and Von Recklinghausen's *osteitis fibrosa cystica* are included in these chapters with questionable justification. The more common conditions, however, of chronic osteomyelitis, Brodie's abscess, Garré's sclerosing osteitis, tuberculosis and syphilis, are well described. A brief review is given of bone diseases of unknown origin, including those dependent upon metabolic disturbances about which definite etiological factors are known, such as rickets and scurvy.

Part II is devoted to "Tumors of Bone." The chapter on osteomas includes hyperostoses, ossifying hematoma and exostoses, in which the distinction between osteochrondromas and osteomas forming in membranous bones are not adequately drawn. This does not detract from the excellence of the photographs chosen to illustrate the various types. In the chapter on chrondromas, the author is on surer ground. This is also true of the chapters on *myositis ossificans* and that devoted to both giant cell tumor and bone cysts. By far the best chapters on bone tumors are those devoted to osteogenic sarcoma. Here the cases and illustrations are well chosen and unusually complete.

This is also true of his discussion of Ewing's sarcoma. Multiple myeloma and metastatic carcinoma are briefly considered.

The entire book is very compact, easily read and forms an excellent introduction to the subject for the student and the busy surgeon. As a reference book many of the entities discussed are too briefly presented and some listed in the author's own classification are entirely omitted, such as chloroma and lipoma.

C. F. G.

Maternal Mortality in New York City. A Study of all Puerperal Deaths—1930–32. By the New York Academy of Medicine Committee on Public Health Relations. 290 pp. $2.00. (*The Commonwealth Fund, New York City, 1933.*)

This octavo volume of 280 pages is an intelligent contribution to both obstetrics and vital statistics. It is unique in investigating and studying deaths at the time of their occurrence when full and exact information is still obtainable from both the attendant and the hospital. This Commonwealth Fund grant was administered by a corps of experts, aided by a special advisory committee of distinguished obstetricians representing the New York Academy of Medicine.

The perennial and cruelly high puerperal death rate in this country motivated the study. In an attempt to improve the situation, this study places the blame where it honestly belongs by dividing the 2,041 deaths into non-preventable and preventable. 65.8 per cent of these deaths were classed as preventable. Of the 1,343 preventable deaths, 61.1 per cent were the fault of the physician, 36.7 per cent due to the patient and only 2.2 per cent to the midwife, despite the fact that she

attended 9.5 per cent of the total births occurring during this three-year period. Among physicians the most culpable group were the surgeons and, after them, the so-called obstetricians. Next to the midwife, the general practitioner was found to be the least dangerous accoucheur. The book concludes with definite recommendations. Among these are: the development of a community conscience in regard to prenatal care: and the instruction of the lay public by physicians "that operative delivery undertaken merely to alleviate pain or shorten labor involves increased risk for mother and baby." The report pleads for the better education of medical students in midwifery, and above all, "to inform the student that the training which he receives does not qualify him to practice as a specialist in obstetrics." To this latter sentiment, all of us who practice and teach obstetrics add a cheerful *Amen.* Finally, the study suggests better facilities to train midwives and recommends that more patients of moderate means should have their babies at home, employing "qualified midwives under the supervision of physicians."

In the main, one must agree with these somewhat startling conclusions. We regret that the study does not include the comparison of maternal mortality occurring in the practice of expertly trained obstetricians with that of poorly trained obstetricians who call themselves experts.

A. F. G.

A Textbook of Laboratory Diagnosis. By EDWIN E. OSGOOD and HOWARD D. HASKINS. 475 pp. $3.00. (*P. Blakiston's Son & Co., Philadelphia, 1931.*)

The subject matter is up to date, the style clear and direct. Part I is informing as to laboratory tests, their indications, contra-indications and sources of error. The details of laboratory technique are presented in Part II. Each chapter is preceded by a brief résumé of essential data in physiology and pathology, and references for collateral reading are given. Some of the illustrations could be improved (such as that of parasites in stools), and others added, but the book as a whole can be very highly recommended.

M. M. W.

Laboratory Medicine. A Guide for Students and Practitioners. By DANIEL NICHOLSON. 2nd edition, thoroughly revised. 124 engravings & 3 colored plates. 566 pp. $6.50. (*Lea & Febiger, Inc., Philadelphia, 1934.*)

The outstanding merit of this book is that the material is up to recent standards. The tests described have been chosen with discrimination for the inexperienced reader. The discussion of methods of stool examination is adequate for localities far removed from the larger medical centers.

M. M. W.

Red Blood Cell Diameters. By CECIL PRICE-JONES. 82 pp. $3.50. (*Oxford University Press, New York, 1933.*)

An assembly of the author's important observations on the diameters of red blood cells in health and disease. There is an interesting historical introduction.

M. M. W.